TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER2-POSITIVE STAGE IV METASTATIC BREAST CANCER – AN OPEN LABELLED RANDOMIZED STUDY

Dissertation Submitted To

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF MEDICINE

IN

PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI -11

MAY – 2019

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER2-POSITIVE STAGE IV METASTATIC BREAST CANCER – AN OPEN LABELLED RANDOMIZED STUDY"** submitted by **DR.S.MOHAMED THAJUDEEN** to the Tamilnadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the requirement for the award of the Degree of Doctor of Medicine in Pharmacology during the academic period 2016-2019 is a bonafide research work carried out by him under direct supervision & guidance.

PROFESSOR AND H.O.D

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DECLARATION

I solemnly declare that the dissertation titled "**TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER2-POSITIVE STAGE IV METASTATIC BREAST CANCER – AN OPEN LABELLED RANDOMIZED STUDY**" is done by me in the Department of Pharmacology, Tirunelveli Medical College, Tirunelveli.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of Doctor of Medicine in Pharmacology.

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REF.NO: 987/PHARMA/2017

PROTOCOL TITLE: TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER-2 POSITIVE STAGE IV METASTATIC BREAST CANCER – A OPEN LABEL RANDOMIZED STUDY
PRINCIPAL INVESTIGATOR: Dr.MOHAMED THAJUDEEN.S. MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: PG STUDENT
DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI

Dear, Dr.MOHAMED THAJUDEEN.S, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 10.03.2017.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed.
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a) The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b) The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c) If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d) If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e) Approval for amendment changes must be obtained prior to implementation of changes.
   f) The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g) Any deviation/violation/waiver in the protocol must be informed.

STANDS APPROVED UNDER SEAL

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CERTIFICATE – II

This is to certify that this dissertation work titled "**TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER2-POSITIVE STAGE IV METASTATIC BREAST CANCER – AN OPEN LABELLED RANDOMIZED STUDY**" of the candidate **DR. S. MOHAMED THAJUDEEN** with registration Number 201616202 for the award of M.D. in the branch of Pharmacology. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **2 percentage** of plagiarism in the dissertation.

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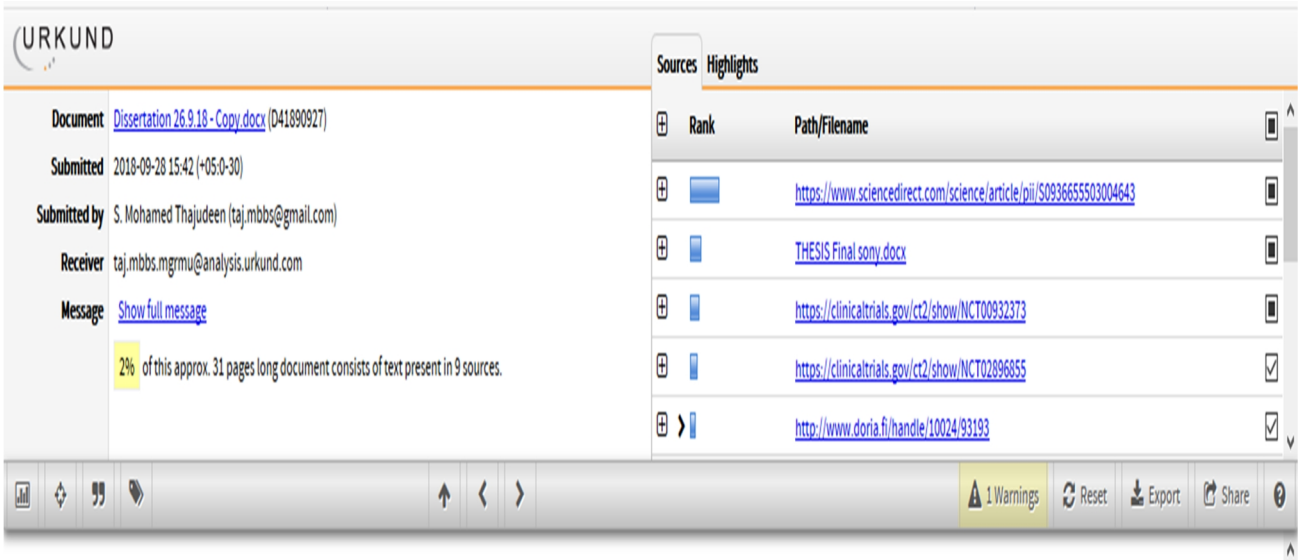

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Dissertation Submitted To THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF MEDICINE IN PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY TIRUNELVELI MEDICAL COLLEGE TIRUNELVELI -11 MAY – 2019

INTRODUCTION Breast cancer is a major public health problem for women throughout the world. Worldwide,

100% #1 Active

is the most frequently diagnosed cancer and the leading cause of cancer death among

External source: http://www.doria.fi/handle/10024/93193 100%

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females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. There is a five-fold variation in incidence between high-incidence areas such as the United States and Western Europe, and low incidence areas such as Africa and Asia. Metastatic relapse is still common and survival of patients with metastatic breast cancer remains poor (1). For patients with advanced breast cancer whose tumors express the estrogen or progesterone receptor, endocrine therapy is the first-line treatment and extends survival (2, 3). For patients with receptor-negative cancers or those whose disease has become resistant to endocrine therapy, chemotherapy is the first-line treatment. Anthracyclines are the standard chemotherapeutic agents for metastatic breast cancer (4). However, some patients do not respond to anthracycline therapy and

CONTENTS

INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. There is a five-fold variation in incidence between high-incidence areas such as the United States and Western Europe, and low incidence areas such as Africa and Asia. Metastatic relapse is still common and survival of patients with metastatic breast cancer remains poor [1]. For patients with advanced breast cancer whose tumors express the estrogen or progesterone receptor, endocrine therapy is the first-line treatment and extends survival [2, 3]. For patients with receptor-negative cancers or those whose disease has become resistant to endocrine therapy, chemotherapy is the first-line treatment.

Anthracyclines are the standard chemotherapeutic agents for metastatic breast cancer [4]. However, some patients do not respond to anthracycline therapy and anthracyclines have severe toxic effects, especially on the heart. Docetaxel is a semisynthetic taxoid derived from the European yew tree, Taxus baccata [5]. It is one of the most active chemotherapeutic agents for treating patients with metastatic breast cancer. Docetaxel is effective both as first-line treatment [6, 7] and as second-line treatment for patients who have received anthracycline- or an alkylating agent-containing chemotherapy [8, 9]. Docetaxel is the only drug which has shown superiority over single-agent anthracycline therapy as well as combination regimens in the metastatic setting [10].

Breast tumors express high levels of growth factors and their receptors, and breast cancer cells appear to exhibit autocrine- or paracrine stimulated growth. Among the best-studied growth factor receptor systems in breast cancer is the one constituted by the ErbB tyrosine kinase receptors (also known as type I receptor tyrosine kinases), comprising the epidermal growth factor (EGF) receptor (ErbB1/EGF receptor/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4)**.**

The human epidermal growth factor receptor 2 gene (HER2) belongs to the ErbB receptor family and has partial homology to the EGF receptor encodes a 185-kD transmembrane glycoprotein receptor (p185HER2) and is amplified in 25%–30% of human breast [(11)]. Disease-free survival (DFS) and overall survival (OS) rate were shorter in patients with HER2 overexpression [(12)]. In addition, several other lines of evidence support a direct role for HER2 in the pathogenesis and clinical aggressiveness of HER2-overexpressing tumors: the introduction of HER2 into non-neoplastic cells causes their malignant transformation; transgenic mice expressing HER2 develop mammary tumors and MAbs directed at the HER2 receptor inhibit the growth of tumors and of transformed cells that express high levels of this receptor.

Trastuzumab (Herceptin; F. Hoffmann-La Roche Ltd, Basel, Switzerland) is a humanized murine monoclonal antibody that binds specifically to the extracellular domain of the HER2 protein. The survival benefit from trastuzumab has been well established in numerous clinical trials of patients with early and metastatic breast cancer who had overexpression of HER2. The use of trastuzumab either in monotherapy or combination with chemotherapy [(13-16)] and endocrine therapy all resulted in survival

benefit [17]. Trastuzumab is most frequently combined with chemotherapy agents including paclitaxel, docetaxel, vinorelbine, gemcitabine and carboplatin [14-16,18].

The clinical efficacy and favorable safety profile of trastuzumab in metastatic breast cancer (MBC) have been demonstrated both as monotherapy [19,20] and combination with the taxane [21,22]. Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, graded by IHC, and/or with HER2 gene amplification, as determined by fluorescence in situ hybridization (FISH). Docetaxel is widely used taxane and is one of the most active chemotherapeutic agents used in the treatment of MBC [23]. Preclinical data indicate synergy between docetaxel and Trastuzumab [24], and clinical activity has been confirmed in a number of phase II studies, with response rates of 44% to 83% and toxicity comparable with that of single-agent docetaxel [25].

While the trastuzumab combination with chemotherapy has been a standard regimen for more than ten years its usage is limited by its high cost. However, more widespread use resulted from Government health insurance schemes for trastuzumab. Only limited number of studies are available about the efficacy and safety of trastuzumab in India because of its high cost. Therefore, this study was designed to compare the efficacy, safety and tolerability of trastuzumab plus docetaxel and docetaxel monotherapy in Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer patients.

REVIEW OF LITERATURE

Breast cancer ranks as the number one cancer among Indian females with rate as high as 25.8 per 100,000 women and mortality of 12.7 per 100,000 women, according to health ministry. According to estimates, at least 17,97,900 women in India may have breast cancer by 2020 [26]. Breast cancer accounts for 27 per cent of all cancers in women in India, with the incidence rising in the early thirties and peaking at ages 50-64 years. It is estimated that 1 in 28 women is likely to develop breast cancer during her lifetime.

Female breast cancer incidence rates vary considerably across racial and ethnic groups. The average annual age-adjusted incidence rate from 2008 to 2012 was 128.1 cases per 100,000 among whites, 124.3 cases among African Americans, 91.9 cases in Hispanics, 91.9 cases in American Indians and Alaska Natives, and 88.3 cases among Asian Americans and Pacific Islanders [27]. Reasons for the higher incidence rates in whites than in other racial and ethnic groups may include differences in reproductive and lifestyle factors and access to and use of screening.

EPIDEMIOLOGY AND ETIOLOGY

Gender

The two variables most strongly associated with the occurrence of breast cancer are gender and age. Although one commonly thinks of breast cancer as a disease confined to women, about 2,600 cases of male breast cancer were diagnosed in the United States in 2016 [27]. Male gender had been considered a poor prognostic factor in some investigations, but it is now believed that higher mortality rates in men are attributable to more advanced disease at the time of diagnosis. Clinical outcome for

male breast cancer is comparable to female breast cancer when stage and other known prognostic factors are controlled [28]. Treatment of breast cancer in men is similar to treatment of breast cancer in women.

Age

The survey carried out by Indian Council of Medical Research (ICMR) in the metropolitan cities during the year 1982 to 2005 showed doubling of the incidence of breast cancer. Indian women having breast cancer are found to be a decade younger than western women suggesting that breast cancer occurs at a younger premenopausal age in India [29]. Cancers in the young tend to be more aggressive. Studies suggest that the disease peaks at 40–50 years in Indian women. Many of these cancers are HER2 positive and ER/PR negative, or HER2/ER/PR all three negative, and have a poor prognosis. In India, majority of patients present at locally advanced or at metastatic stages at the time of diagnosis. According to various studies, majority of patients with carcinoma breast report in stages I and II of disease in west, whereas in India 45.7% report only in advanced stages [30]. Disease presentation in such conditions results in increased mortality in India. Data from UK cancer registry showed an increasing trend for breast cancer from age 30 to 35 achieving highest peak during age 60–65 years, suggesting that an average woman in India under the age of 40 has a considerably higher chance of developing the disease than United Kingdom [31].

Endocrine Factors

A number of endocrine factors have been linked to the incidence of breast cancer [32,33]. Many of these relate to the total duration of menstrual life.

Early menarche, generally defined as menstruation beginning before age 12 years, increases the cumulative lifetime risk of breast cancer development. Similarly, a late age of natural menopause (age 55 years or later) increases the risk of breast cancer development, although to a lesser degree than early menarche [32]. Conversely, bilateral oophorectomy before age 40 years reduces the risk of developing breast cancer.

Nulliparity and a late age at first birth (greater than or equal to 30 years) are reported to increase the lifetime risk of developing breast cancer. It is suggested that the period between the onset of menses and the age of first pregnancy provides a "window of initiation" for the development of breast cancer. This is a time when an unbalanced hormonal environment reacts with the abundant and highly responsive breast tissue. Investigators postulate that international differences in age of menarche, age at menopause, and childbearing may account for a substantial part of the international differences in the incidence of breast cancer.

Many studies have evaluated the relationship between exogenous hormones and the development of breast cancer. A longer duration of HRT and concurrent use of progestins appear to contribute to breast cancer risk. In addition, the impact of HRT use on breast cancer risk also varies according to race, body mass index (BMI), and breast density [34]. The use of postmenopausal HRT in women with a history of breast cancer is generally contraindicated. Epidemiologic studies of oral contraceptives do not show a consistent relationship between use of birth control pills and breast cancer risk. Results are conflicting, and assessment of the studies should consider the particular oral contraceptive products involved, daily and cumulative doses of the hormones administered, and latency period for development of breast cancer. A meta-analysis of

13 prospective cohort studies conducted between the years of 1989 and 2010 reported a nonsignificant increase in breast cancer incidence for patients who used oral contraceptives compared with those who had never used oral contraceptives [35]. It is also important to note that oral contraceptives are known to reduce the risk of ovarian and endometrial cancers. Most experts believe that the safety and benefits of low-dose oral contraceptives currently outweigh the potential risks.

Genetic Factors

Both personal and family histories influence a woman's risk of developing breast cancer. A personal history of breast cancer is associated with an increased risk of developing contralateral breast cancer. Cancers of the uterus and ovary are also associated with an increased risk of developing breast cancer. A number of cancer family syndromes include breast cancer in association with other types of cancers.

Germ-line mutations in either BRCA1 or BRCA2 are associated with an increased risk for breast and ovarian cancer. These genes function as tumor suppressor genes, maintaining genomic integrity and DNA repair. Compared with an average woman's 13% lifetime risk of developing breast cancer, the probability of developing breast or ovarian cancer by the age of 70 years in women with a BRCA1 or BRCA2 mutation is estimated to be 57% and 49% for breast cancer and 40% and 18% for ovarian cancer, respectively [36].

Although most genetic causes of breast cancer are attributed to BRCA1 and BRCA2, other genes that have been identified as being associated with hereditary breast cancer include TP53, CHEK2, PALB2, PTEN, ATM, and others [37].

Environmental and Lifestyle Factors

Breast cancer incidence rates vary considerably among countries, which suggests that environmental and lifestyle factors play an important role in the etiology.

Diet

Diet is an important and modifiable environmental risk factor. Possible relationships between fat intake and steroid hormone metabolism have led to an emphasis on dietary fat as a possible etiologic agent for breast cancer.

An additional dietary factor to be explored in the breast cancer population includes food-derived heterocyclic amines, which are known carcinogens found commonly in cooked red meat or processed meat.

Another dietary factor that deserves mention is the possible effect of phytoestrogens on breast cancer risk. Phytoestrogens are natural plant estrogens found in soybean products, seeds, berries, and nuts. Because these compounds exhibit weak estrogenic properties, some experts believe that they may function as relative antiestrogens by displacing natural estradiol.

Anthropometric factors

Both body weight and height are associated with the incidence of breast cancer. Most studies of premenopausal women show either no relationship with body weight or slightly declining breast cancer risks with increasing body weight. Most studies in postmenopausal women show increasing breast cancer risks with increasing body weight.

Physical activity

Increased physical activity can reduce breast cancer risk because of its potential effects on reducing endogenous estrogen/progesterone levels. The physiologic mechanisms to reduce cancer risk are thought to be different in pre and postmenopausal women. In young women, intense exercise delays the onset of menarche and increases the probability of anovulatory cycles, thus reducing exposure to estrogens and progesterone. In postmenopausal women, physical activity indirectly reduces breast cancer risk by decreasing percent body fat, and thus lowering circulating estrogens.

Alcohol

Many epidemiologic studies have evaluated the relationship between alcohol and breast cancer. Studies indicate both a modest positive association between alcohol and breast cancer and a dose–response relationship [38]. The risk increases with consumption of alcohol in general regardless of the beverage type or woman's menopausal status. Although the exact mechanism is unknown, the most plausible biologic hypothesis relates to increased levels of estrogen or other reproductive steroid hormones caused by impaired liver function.

Radiation

Radiation to the breast tissue is associated with an increased risk of breast cancer, particularly with exposure at a young age (less than 20 years), again suggesting that a "window of initiation" for breast cancer occurs at a relatively early age. Women treated with chest irradiation for Hodgkin lymphoma in childhood or adolescence and survivors of other childhood cancers (in which radiation is used as a mainstay of therapy) are

among the populations at greater risk for secondary breast cancers. The risk increases linearly with radiation dose. Exposure to diagnostic x-rays, including annual screening mammography, does not impart a sufficient dose of radiation for clinical concern in the general population. However, the risk of breast cancer after radiation exposure even in low levels in those with genetic risk factors is unclear and is an ongoing area of research.

Smoking

Tobacco smoke exposure has not been associated with an increased risk of breast cancer in the past. In recent years, some studies have found that heavy smoking in certain groups is linked to a higher risk, such as in women who started smoking before having their first child [39].

CLINICAL PRESENTATION

General

The patient may not have any symptoms because breast cancer may be detected in asymptomatic patients through routine screening mammography.

Local Signs and Symptoms

A painless, palpable lump is most common.

Less common: pain; nipple discharge, retraction, or dimpling; skin edema, redness, or warmth.

Palpable local–regional lymph nodes may also be present.

Signs and Symptoms of Systemic Metastases

Depends on the site of metastases, but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, or mental status changes.

Laboratory Tests

Tumor markers such as cancer antigen (CA 27.29) or carcinoembryonic antigen (CEA) may be elevated.

Alkaline phosphatase or liver function test results may be elevated in patients with metastatic disease.

Other Diagnostic Tests

1. Mammography (with or without ultrasonography, breast MRI, or both).
2. Biopsy for pathology review and determination of tumor ER or PR status and human epidermal growth factor receptor-2 (HER2) status.
3. Systemic staging tests may include chest radiography, chest computed tomography (CT), bone scan, abdominal CT or ultrasonography, or MRI.

Significant advances in the safety and efficacy of screening mammography have occurred during the last 2 decades. These advances have enabled superior visualization of breast and breast tissue with a lower dose of radiation being delivered. Despite these advances, about 10% of all palpable masses are not detected by mammography. This is most commonly observed in premenopausal women and may be directly related to the increased density of breast tissue in this estrogen-rich environment. In addition,

differences exist between breast imaging quality and interpretation, and it is best to have imaging conducted at the same facility over time if possible.

Stage Evaluation

A painless lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. In small numbers of cases, stabbing or aching pain is the first symptom. Less commonly, nipple discharge, retraction, or dimpling may herald the onset of the disease. In more advanced cases, prominent skin edema, redness, warmth, and induration of the underlying tissue may be observed.

Breast cancer that is confined to a localized breast lesion is often referred to as early, primary, localized, or curable. Breast cancer that has spread to local–regional lymph nodes is still considered early stage. Unfortunately, breast cancer cells often spread by contiguity, through lymph channels, and through the blood to distant sites. This often occurs early in breast cancer growth, and deposits of tumor cells form in distant sites that are undetected with current diagnostic methods and equipment (micrometastases). When breast cancer cells can be detected clinically or radiologically in sites distant from the breast, the disease is referred to as advanced or metastatic breast cancer (MBC).

Tissues most commonly involved with distant metastases are lymph nodes (other than local–regional lymph nodes), skin, bone, liver, lungs, and brain. Symptoms of bone pain, difficulty breathing, abdominal enlargement, jaundice, and mental status changes may herald the clinical presentation of MBC. A small percentage of women have signs

and symptoms of distant metastases when they first seek treatment. In virtually all of them, a neglected breast mass has been present for several months to years. In addition, 10% to 50% of all patients who initially are treated for localized disease eventually develop signs and symptoms of MBC [40].

DIAGNOSIS

The initial workup for a woman presenting with a breast mass or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional mammography, and possibly other breast imaging techniques such as ultrasonography or MRI.

Mammography

Most breast cancers can be visualized on a mammogram as a mass, a cluster of calcifications, or a combination of these findings. Specific mammographic features associated with the highest risk of malignancy include masses with spiculated margins or an irregular shape and calcifications with a linear or segmental distribution [41]. One major factor that affects the ability of mammography to detect cancer includes breast density (the fat-to-glandular tissue ratio of the breast), which may be affected by age, menopausal status, and HRT use. Ultrasonography, MRI, and digital mammography are alternate breast imaging methods that are being investigated for women with dense breasts or other specific subsets of patients with breast cancer (eg, MRI in patients with inflammatory breast cancer [IBC]) [42]. The technical quality of the examination and the expertise of the radiologist are also important factors.

Biopsy

Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

Three techniques are available: fine-needle aspiration, core-needle biopsy, and excisional biopsy [43].

Excisional biopsy completely removes the abnormal tissue.

Needle biopsies are performed percutaneously and include both core-needle biopsy (which removes a core of tissue) and fine-needle aspiration (which removes cells from the suspicious site). Core-needle biopsy is the preferred biopsy method for mammographically detected, nonpalpable abnormalities [44]. Core-needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and can distinguish invasive from in situ breast cancer (which fine needle biopsy cannot). After confirmation of malignancy via core-needle biopsy, subsequent surgical procedures are performed (either before or after systemic therapy) to assure complete removal of the abnormal tissue.

STAGING AND PROGNOSIS

Breast cancer stage is defined on the basis of the primary tumor extent and size (T1-4), presence and extent of lymph node involvement (N1-3), and presence or absence of distant metastases (M0-1).

STAGING OF BREAST CANCER

Primary Tumor (T)

T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor ≤2 cm
T1a	Tumor >0.1 cm but ≤0.5 cm
T1b	Tumor >0.5 but ≤1 cm
T1c	Tumor >1 cm but ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Extension to chest wall, inflammation, satellite lesions, ulcerations

Regional Lymph Nodes (N)

PN0(i–)	No regional lymph node metastasis histologically, negative IHC
PN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
PN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
PN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
PN1	Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
PN1mi	Micrometastasis (>0.2 mm, none >2 mm)
PN1a	Metastasis in one to three axillary lymph nodes
PN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[a]
PN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.[a] (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral subcarinal lymph nodes

Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis (includes spread to ipsilateral supraclavicular nodes)		
Stage Grouping			
Stage 0	TIS	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Stage 0

Carcinoma in situ (Tis) or disease that has not invaded the basement membrane of the breast tissue.

Stage I

Small primary invasive tumor without lymph node involvement or with micrometastatic nodal involvement.

Stage II

Disease usually involves regional lymph nodes. Stages I and II are often referred to as early breast cancer. It is in these early stages that the disease is highly curable (99% 5-year survival in patients with disease confined to the breast, node negative) [45].

Stage III

Referred to as locally advanced disease, usually represents a large tumor with extensive nodal involvement in which either node or tumor is fixed to the chest wall.

Stage IV

Disease is characterized by the presence of metastases to organs distant from the primary tumor and is often referred to as advanced or metastatic disease as described earlier (26% 5-year survival rate in patients with distant metastases) [46].

Staging for breast cancer is separated into two groups, clinical and pathologic.

Clinical staging is assigned before surgery and is based on physical examination (assessment of tumor size and presence of axillary lymph nodes), imaging (mammography, ultrasonography, and so on), and pathologic examination of tissues (eg, biopsy results). ***Pathologic staging*** occurs after surgery and uses information from clinical staging but adds data from surgical exploration and resection, such as tumor size at surgery and the involvement of micro- or macro-invasive tumor in the lymph nodes or other metastatic sites.

PATHOLOGY

The pathologic evaluation of breast tissue serves to establish histologic diagnosis and to confirm the presence or absence of other factors believed to influence prognosis.

Invasive Carcinoma

Invasive breast cancers are a histologically heterogeneous group of lesions. Most breast cancers are adenocarcinomas and are classified on the basis of their microscopic

appearance as ductal or lobular, corresponding to the ducts and lobules of the normal breast. The various histologic types of breast cancer have different prognoses, but it is unknown whether their response to therapy differs because patients in therapeutic trials are not typically stratified according to histologic type. The five most common types of invasive breast cancer are as follows [47].

1. Invasive or infiltrating ductal carcinoma

Most common histology, accounting for about 75% of all invasive breast cancers. These tumors commonly spread to the axillary lymph nodes, and their prognosis is poorer than for some other histologic types. Invasive or infiltrating lobular carcinoma accounts for 5% to 10% of breast tumors. Both clinical and radiologic findings for these tumors may be quite subtle. The typical presentation is an area of ill-defined thickening in the breast in contrast to a prominent lump characteristic of infiltrating ductal carcinoma.

2. Infiltrating lobular carcinoma

More difficult to detect by mammography. Overall, infiltrating lobular carcinoma and infiltrating ductal carcinoma have similar likelihoods of axillary node involvement and disease recurrence and death, yet the sites of metastases may differ. Whereas infiltrating ductal carcinoma more frequently metastasizes to the bone or to the liver, lung, or brain, infiltrating lobular carcinoma tends to metastasize to the leptomeninges, peritoneal surfaces, retroperitoneum, gastrointestinal tract, reproductive organs, and other unusual sites.

The three most common special types of invasive cancer are medullary, mucinous, and tubular. The prognosis may be more favorable with these unusual histologies.

3. Medullary carcinoma accounts for fewer than 7% of all breast carcinomas

4. Mucinous (or colloid) carcinoma constitutes about 3%, and

5. Tubular carcinoma accounts for about 2% of all breast cancers.

Histologies rarely reported include adenocystic carcinoma, carcinosarcomas, metaplastic, cribriform, and papillary carcinoma.

Special situations seen clinically and histologically include Paget's disease of the breast, phyllodes tumors, and Inflammatory Breast Cancer (IBC).

Paget's disease of the breast occurs in 1% to 4% of all patients with breast cancer and is characterized by neoplastic cells in the nipple areolar complex. The patient presents clinically with eczematous changes in the nipple with itching, burning, oozing, bleeding, or some combination of these. In most cases, the nipple changes are associated with an underlying carcinoma in the breast.

Phyllodes tumors of the breast (also known as cystosarcoma phyllodes) are rare tumors with subtypes that range from benign to malignant. These tumors often enlarge rapidly, are painless, and can appear as fibroadenomas [(48)].

IBC is characterized clinically by prominent skin edema, redness and warmth, and induration of the underlying tissue. Biopsies of the involved skin reveal cancer cells in the dermal lymphatics. IBC typically has a very rapid onset and is often mistaken for

an infectious cellulitis or mastitis. Although it may look somewhat similar to a neglected mass, its presentation with rapid onset and progression of local symptoms distinguishes it from other cases of locally advanced breast cancer. The prognosis of patients with IBC is poor even if the disease is apparently localized [49].

Noninvasive Carcinoma

Noninvasive lesions may be divided broadly into ductal and lobular categories. Evidence supports that the development of malignancy is a multistep process and that invasive breast cancer has a preinvasive, in situ phase. During the carcinoma in situ phase, normal epithelial cells undergo genetic alterations that result in malignant transformation. Transformed epithelial cells proliferate and pile up within lobules or ducts but lack the required genetic alterations that enable the cells to penetrate the basement membrane. Therefore, carcinoma in situ is diagnosed when malignant transformation of cells has occurred but the basement membrane is intact.

The widespread use of screening mammography with subsequent biopsy and greater recognition of noninvasive breast carcinoma by pathologists has resulted in a significant increase in the diagnosis of in situ breast cancer over the past decade. An estimated 61,000 new cases of female noninvasive (in situ) breast cancer is expected to be diagnosed in 2016 [27]. The natural history of these disorders is not well described, and thus the debate continues regarding carcinoma in situ: Is carcinoma in situ preinvasive cancer or simply a marker of unstable epithelium that represents an increased risk for the development of subsequent aggressive cancer? [50] Answering this question may change the way noninvasive breast cancers are treated.

Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ (DCIS) is more frequently diagnosed than lobular carcinoma in situ (LCIS). Most cases of DCIS today are found by biopsies performed for clustered microcalcifications seen on screening mammography, a hallmark of this disorder.

The ultimate goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease. If left untreated, it is estimated that 14% to 50% of DCIS lesions will progress to invasive breast cancer [(50)]. Therefore, up to 50% of these tumors do not progress to invasive disease, but identifying this group of patients is not yet feasible, and all diagnoses should be treated. Locoregional treatment of DCIS depends on its location, size, and pathology [(49)].

Treatment options include

(a) Local excision alone with negative margins,

(b) Local excision (with negative margins) followed by breast irradiation, and

(c) Traditional total mastectomy with or without reconstruction. Whole-breast irradiation is recommended after excision to significantly decrease the risk of local recurrence, although there is no evidence that survival differs between the previously mentioned options [(49)]. Excision with negative margins alone without radiation may be considered in patients with small and low-grade DCIS. Mastectomy had been the standard treatment of DCIS for several decades, but long-term survival appears to be equivalent with mastectomy versus local excision and irradiation, and the latter option allows for breast conservation. If more than one area of the breast is involved with

DCIS, a mastectomy is the preferred option. Axillary lymph node dissection (ALND) is generally not indicated, although SLNB may be considered in selected patients [48]. Cytotoxic chemotherapy has no role in the treatment of patients with pure DCIS. It is important to determine hormone receptor status on the cancer cells. Tamoxifen treatment for 5 years may be considered in some women with hormone receptor–positive DCIS. The NSABP B-24 trial, which randomized women with DCIS to lumpectomy with radiation plus either tamoxifen or placebo, showed a benefit with tamoxifen in reducing ipsilateral breast cancer recurrence (32% reduction; p=0.025). Further subgroup analyses of this trial showed a benefit for patients with ER-positive DCIS [51]. The NSABP B-35 trial evaluated the role of the AI anastrozole compared to tamoxifen each given for 5 years in the treatment of postmenopausal hormone receptor–positive DCIS in patients who had lumpectomy with radiation therapy. Significant improvement in 10 year point estimates for the breast cancer-free interval was seen with anastrozole (89.1% for tamoxifen and 96.3% for anastrozole, HR, 0.73; p=0.02). Further subgroup analyses of this trial showed the benefit to be primarily in women less than 60 years of age. These decisions are often difficult to discuss with patients because these treatments have toxicities that are worrisome. Nonetheless, an open and honest conversation regarding the risks and benefits is warranted.

Lobular carcinoma in situ (LCIS)

LCIS is a microscopic diagnosis. In these cases, there is generally no palpable mass, and no specific clinical abnormality is noted. Unlike DCIS, LCIS does not generally demonstrate calcifications on mammography and in fact is usually undetectable by mammography. Consequently, the diagnosis of LCIS is usually an

incidental finding in biopsy specimens obtained because of symptoms or mammography findings consistent with benign lesions. It is unclear whether LCIS is a precursor lesion to invasive carcinoma or serves as a marker of risk for invasive carcinoma developing somewhere in the breast. The risk for developing invasive carcinoma is about 0.5% to 1% per year, and both invasive ductal carcinoma and invasive lobular carcinoma can occur. In about 50% to 70% of patients, there are multiple foci of LCIS in the ipsilateral breast, and the contralateral breast is also affected. Thus, the risk for the development of breast cancer is equally high in either breast, which makes the management of LCIS very controversial [52]. Some experts favor a program of observation, with semiannual physical examination and annual mammography [48]. In selected patients with high-risk genetic mutations or strong family history and in women who are particularly anxious about the development of cancer, bilateral mastectomies with or without reconstruction may be considered [43]. Radiation and systemic chemotherapy have no role in the management of LCIS. The use of chemoprevention with tamoxifen in premenopausal women or tamoxifen, raloxifene, or exemestane in postmenopausal women may also be considered for risk reduction in these patients [44].

PROGNOSTIC FACTORS

The natural history of breast cancer varies among patients, with some having extremely aggressive disease that progresses rapidly and others following a more indolent course. The ability to predict prognosis is extremely important in designing treatment recommendations to maximize quantity and quality of life. A number of pathologic prognostic and predictive factors have been identified. Prognostic factors are

characteristics or measurements available at diagnosis or time of surgery that in the absence of adjuvant systemic therapy are associated with recurrence rate, death rate, or other clinical outcomes. Predictive factors are measurements available at diagnosis that are associated with response to a specific therapy. Prognostic and predictive factors fall into three general categories:

(a) Patient characteristics that are independent of the disease such as age;

(b) Cancer characteristics such as tumor size or histologic type; and

(c) Other biomarkers that are measurable parameters in tissues, cells, or fluids, such as hormone receptor status.

Ideally, the use of prognostic and predictive factors can limit a specific treatment to patients who are most likely to derive benefit, thus sparing unwanted toxicities in those who are unlikely to benefit.

Patient characteristics

Age at diagnosis and ethnicity are patient characteristics that may affect prognosis. Some younger patients, particularly those younger than 35 years of age, have more aggressive forms of breast cancer and a worse prognosis. Younger patients are more likely to present with poor prognostic features, such as affected lymph nodes, large tumor size, and tumors negative for hormone receptors. Race and ethnicity may also play a role in breast cancer prognosis. African American women have decreased survival periods compared with white women. The cause of this racial disparity is widely debated, with possible explanations including access to care, socioeconomic

status, cultural differences, higher stage at diagnosis, and more aggressive biologic features.

Potentially modifiable prognostic factors include alcohol use, dietary factors, weight, and exercise. The association between breast cancer prognosis and alcohol consumption is not as strong as with alcohol and breast cancer risk. A review of seven observational studies showed that postdiagnosis alcohol consumption was not associated with breast cancer outcomes [54]. Two randomized controlled studies examined the effects of diet on the risk of breast cancer with conflicting results, primarily focusing on lowering dietary fat [55,56]. One study found an improvement in disease-free survival (DFS) with incorporation of a low-fat diet (less than 15% dietary fat per day vs no intervention) [56], but another study found no difference in recurrence rates between two dietary intervention approaches (both incorporating a low-fat, high-fiber approach) [55]. Although these studies asked different questions and had many confounding variables that potentially affected the results, most clinicians recommend that breast cancer survivors eat a low-fat, high-fiber diet and maintain a healthy weight. Obesity at the time of a breast cancer diagnosis has been shown to increase the risk of breast cancer– specific and overall mortality compared with nonobese breast cancer patients, although the impact of weight loss in this population is unclear [54]. Observational studies have reported that exercise in women after a diagnosis of breast cancer may also decrease the likelihood of breast cancer recurrence and breast cancer–related death [54]. Based on these data, agencies such as the ACS have recognized that physical activity, weight control, and diet are potentially modifiable risk factors for

reducing the risk of recurrent breast cancer and other comorbidities (eg, heart disease, diabetes) [57].

Cancer characteristics

Disease characteristics that have been shown to provide important prognostic information include lymph node status, tumor size, histologic subtype, nuclear or histologic grade, lymphatic and vascular invasion (LVI), and proliferation indices.

Tumor size and the presence and number of involved lymph nodes are established primary factors in assessing the risk for breast cancer recurrence and subsequent metastatic disease.

The number of affected lymph nodes is directly related to the risk of disease recurrence. The revised staging system for breast cancer recognizes the absolute number of positive nodes as a prognostic factor: N1 represents one to three positive nodes, N2 represents four to nine positive nodes, and N3 represents 10 or more positive nodes in its pathologic staging system [58].

The relationship between tumor size and lymph node status is complex and not a simple grouping.

Certain histologic subtypes and clinical presentation of breast cancer have prognostic importance. As mentioned earlier, because women with pure tubular or mucinous tumors have more favorable outcomes than those with invasive ductal carcinomas, treatment recommendations may differ [48]. IBC, although a clinical designation and not a distinct histologic subtype, is associated with a poor prognosis [49].

Nuclear grade and tumor (histologic) differentiation are known independent prognostic indicators. Several histologic grading systems have been developed, most of which grade tumors with a score from 1 to 3: grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. Higher grade tumors are associated with higher rates of distant metastasis and poorer survival. This factor aids in making treatment decisions, particularly for patients with small tumors and negative lymph nodes.

Lymphatic and vascular invasion (LVI), defined as evidence of tumor emboli in lymphatic or vascular spaces, is a poor prognostic factor likely representing ability of the cancer to spread via hematogenous routes. However, the utility of this as a prognostic factor is largely unknown and is not currently included in either staging or treatment guidelines [58].

Biomarkers

The rate of tumor cell proliferation also is associated with risk of breast cancer recurrence. Rate of cell proliferation can be evaluated with various techniques, including

(1) mitotic index, which counts the number of mitotic bodies;

(2) thymidine-labeling index or S-phase fraction with DNA flow cytometry, which determines the percentage of tumor cells actively dividing; or

(3) the use of monoclonal antibodies (MoABs) to antigens present on proliferating cells, such as Ki-67. In a meta-analysis of 85 studies and nearly 33,000 patients, proliferation markers (including Ki-67, mitotic index, proliferating cell nuclear antigen, and

thymidine or bromodeoxyuridine labeling index) were associated with significantly shorter disease-free and OS periods [59]. These proliferation indices are additional factors that may be useful in decision making and may predict for responsiveness to chemotherapy, although this is still controversial.

Hormone receptors

Hormone receptors are not strong prognostic markers but are used clinically to predict response to endocrine therapy. Hormone receptors are nuclear transcription factors that, upon ligand binding, activate a variety of signal transduction pathways that result in cell growth and proliferation. Determination of both ER and PR status is an established procedure that is important in the management of breast cancer. Immunohistochemistry is used to determine the level (ie, quantity) of hormone receptors, which is important for predictive ability. Other methods of determining ER and PR status, such as mRNA expression, are under investigation but have not been validated as predictive markers. Hormone receptors are most valuable in predicting response to endocrine therapy. About 60% to 70% of patients with ER-positive and PR-positive tumors will respond to hormonal manipulation. More recently, the importance of PR has come under question because response to tamoxifen has been shown to be related to ER status independent of PR status. Guidelines for testing of ER and PR status are available and recommend standards for what tumors to test and methodologic guidelines for pathologists [60]. The majority of patients with primary or MBC have hormone receptor–positive tumors. Hormone receptor positivity, more common in postmenopausal women, is associated with a higher response to endocrine therapy and a longer DFS.

The HER2/neu gene is located on chromosome 17q21 and encodes a 185-kilodaton transmembrane tyrosine kinase growth factor receptor. The HER2 protein is normally expressed at low levels in the epithelial cells of normal breast tissue. HER2 is a member of the HER growth factor receptor family, and its overexpression is associated with transmission of growth signals that control aspects of normal cell growth and division. HER2 overexpression occurs in about 20% to 30% of breast cancers and is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality rates. In some studies, HER2 gene amplification and protein overexpression, measured by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), respectively, correlates with factors associated with a poor prognosis. HER2-positive status clearly predicts response to anti-HER2 therapy. Tumors that are either IHC 3+ or FISH positive for gene amplification are considered to be positive for HER2 [61]. For equivocal results of IHC (2+) or FISH, confirmatory testing with the alternate test is recommended. HER2 gene amplification or protein overexpression has traditionally been considered a poor prognostic factor. However, more recent data suggest that patients with HER2-positive MBC treated with trastuzumab, a MoAB directed against the extracellular domain of the HER2 receptor, have improved survival rates compared with patients with HER2-negative MBC or patients with HER2-positive MBC who do not receive Trastuzumab [62]. These results demonstrate the powerful impact trastuzumab therapy has made on improving patient outcomes.

Although there is a growing understanding of the prognostic significance of individual factors, it is not clear how each factor contributes to the overall prognosis for

an individual patient. Computer-aided models, including Adjuvant! (www.adjuvantonline.com), are available that combine patient- and tumor-related variables to estimate overall prognosis for individual patients with early stage breast cancer (ESBC) and aid in decisions regarding adjuvant systemic therapy [63].

Genetic profiling is also being used to provide prognostic and predictive information on clinical outcomes of breast cancer [64].

Novel molecular markers that have shown prognostic and predictive significance include urokinase-type plasminogen activator and its inhibitor, plasminogen activator inhibitor type 1, cyclin E, and the presence of tumor cells in bone marrow or circulating blood [65]. Prospective validation studies will determine whether these tests can be used to assist decision making in individual patients.

In summary, lymph node status and tumor size are two significant prognostic factors that assist clinicians in estimating prognosis and making treatment recommendations for most breast cancer patients. Although the risk of recurrence is clearly high in patients with large primary tumors or lymph node–positive disease, many patients with small primary tumors and lymph node–negative disease will still develop metastases, yet our ability to accurately identify these individual patients is limited. Evaluation of additional prognostic factors can help identify which patients will have a good outcome with local therapy alone and which patients with aggressive features who would benefit from more aggressive, multimodality treatment. Despite these markers, a large proportion of patients will likely be treated unnecessarily with systemic adjuvant therapy, and better prognostic and predictive tools are needed to better select patients to undergo these toxic and costly treatments and procedures.

TREATMENT

BREAST CANCER STAGE I & STAGE II DISEASE

The management of primary breast cancer has undergone a remarkable evolution as a result of the major efforts at early diagnosis (through encouragement of self-examination as well as through the use of cancer detection centers) and the implementation of combined modality approaches incorporating systemic chemotherapy as an adjuvant to surgery and radiation therapy.

Stage I Breast cancer

Small primary tumors and negative axillary lymph node dissections are currently treated with surgery alone, and they have an 80% chance of cure. *Breast-conserving therapy (BCT)* includes removal of part of the breast, surgical evaluation of the axillary lymph node basin, and radiation therapy to the breast. The amount of breast tissue removed as a part of BCT varies from just removing the cancerous "lump" (a lumpectomy) with a small margin of adjacent normal-appearing tissue to removing the "lump" with a wider excision of adjacent normal-appearing tissue (a wide local excision) to removing the entire quadrant of the breast that includes the cancerous "lump" (a quadrantectomy). All of these techniques are referred to as a *segmental or partial mastectomy.* A meta-analysis of 18 clinical trials in almost 10,000 women found no difference in OS for patients who received BCT compared with mastectomy [66]. However, this and other meta-analyses have suggested the potential for a small increase in the risk of locoregional recurrence with BCT [66, 67].

Node-positive Breast cancer

High risk of both local and systemic recurrence. Thus, lymph node status directly indicates the risk of occult distant micrometastasis. In this situation, postoperative use of systemic adjuvant chemotherapy with six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF protocol) or of fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been shown to significantly reduce the relapse rate and prolong survival. Alternative regimens with equivalent clinical benefit include four cycles of doxorubicin and cyclophosphamide and six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Each of these chemotherapy regimens has benefited women with stage II breast cancer with one to three involved lymph nodes.

Data from a single randomized trial suggest that ALND after SLNB in women with clinically node negative tumors smaller than 5 cm, fewer than three involved sentinel lymph nodes, and undergoing BCT with subsequent breast irradiation resulted in higher morbidity, no improvement in local recurrence, and no difference in DFS or OS with SLNB alone [(68)]. Therefore, the ASCO guidelines currently recommend that clinicians should not recommend ALND for women with ESBC with one or two positive sentinel lymph nodes who will receive BCT followed by radiation [(69)]. Women undergoing mastectomy with positive sentinel lymph nodes should be offered ALND. In studies that incorporated completion axillary dissections for comparison, the SLNB procedure accurately predicted the status of the remaining axillary nodes in more than 90% of patients. Women with large tumors (greater than 5 cm) or locally advanced disease, IBC, or DCIS when BCT is planned should not receive SLNB [(70)].

Women with four or more involved nodes have had limited benefit thus far from adjuvant chemotherapy. Long-term analysis has clearly shown improved survival rates in node-positive premenopausal women who have been treated aggressively with multiagent combination chemotherapy [71, 72].

The results from three randomized clinical trials clearly show that the addition of trastuzumab, a monoclonal antibody directed against the HER-2/neu receptor, to anthracycline- and taxane-containing adjuvant chemotherapy benefits women with HER-2-overexpressing breast cancer with respect to disease-free and overall survival [73].

Breast cancer was the first neoplasm shown to be responsive to hormonal manipulation. Tamoxifen is antiestrogenic in breast cancer cells, but it appears to have estrogenic properties in other tissues and organs [74, 75]. More recent studies show that tamoxifen and other similar drugs have many estrogenic and antiestrogenic effects that depend on the tissue and the gene in question, and they are more appropriately called SERMs. Women receiving adjuvant tamoxifen therapy have reduced risk of recurrence and mortality compared with women not receiving adjuvant tamoxifen therapy [76].

Tamoxifen is beneficial in postmenopausal women when used alone or in combination with cytotoxic chemotherapy. The present recommendation is to administer tamoxifen for 5 years of continuous therapy after surgical resection. Longer durations of tamoxifen therapy do not appear to offer additional clinical benefit.

Postmenopausal women who complete 5 years of tamoxifen therapy should be placed on an aromatase inhibitor such as anastrozole for at least 2.5 years, although the

optimal duration is unknown. In women who have completed 2–3 years of tamoxifen therapy, treatment with an aromatase inhibitor for a total of 5 years of hormonal therapy is now recommended.

Results from several randomized trials for breast cancer have established that adjuvant chemotherapy for premenopausal women and adjuvant tamoxifen for postmenopausal women are of benefit to women with stage I (node-negative) breast cancer. While this group of patients has the lowest overall risk of recurrence after surgery alone (about 35–50% over 15 years), this risk can be further reduced with adjuvant therapy.

STAGE III & STAGE IV DISEASE

The approach to women with advanced breast cancer remains a major challenge, as current treatment options are only palliative. Combination chemotherapy, endocrine therapy, or a combination of both results in overall response rates of 40–50%, but only a 10–20% complete response rate.

Locally Advanced Breast Cancer (Stage III)

Locally advanced breast cancer generally refers to breast carcinomas with significant primary tumor and nodal disease but in which distant metastases cannot be documented.

The natural history of locally advanced breast cancer shows that even when local–regional control is accomplished, systemic relapse and death from breast cancer eventually occur in most patients if systemic therapy is not used [77]. That observation led to interest in the use of neoadjuvant or primary chemotherapy in locally advanced

breast cancer, which renders inoperable tumors resectable and can increase rates of BCT. The NCCN guidelines addressing the management of locally advanced disease recommend primary chemotherapy with an anthracycline- and taxane-containing regimen [78].

After neoadjuvant chemotherapy, most tumors respond with more than a 50% decrease in tumor size; about 70% of patients experience a reduction in their stage of disease. The chemotherapy regimens used in this setting are similar to those used in the adjuvant setting, but generally include an anthracycline and incorporate a taxane in some manner. For patients with HER2-positive tumors, the incorporation of trastuzumab and pertuzumab with chemotherapy is appropriate [79]. Neoadjuvant endocrine therapy may be an option for patients who have unresectable hormone receptor–positive tumors who are unable to receive chemotherapy (eg, multiple comorbid conditions) [80].

Metastatic Breast Cancer (MBC) (Stage IV)

Treatment of MBC with cytotoxic, biologic, or endocrine therapy often results in regression of disease and improvements in quality of life. The choice of therapy for metastatic disease is based on the presence or absence of certain tumor or patient characteristics and extent of disease involvement. The most important factors predicting response to therapy are the presence of HER2, estrogen, and progesterone receptors in the primary tumor tissue.

Breast cancers expressing estrogen receptors (ER) or progesterone receptors (PR) retain the intrinsic hormonal sensitivities of the normal breast—including the

growth-stimulatory response to ovarian, adrenal, and pituitary hormones. Patients who show improvement with hormonal ablative procedures also respond to the addition of tamoxifen. The aromatase inhibitors anastrozole and letrozole are now approved as first-line therapy in women with advanced breast cancer whose tumors are hormone receptor–positive. In addition, these agents and exemestane are approved as second-line therapy following treatment with tamoxifen.

For the 25–30% of breast cancer patients whose tumors express the HER-2/neu cell surface receptor [81], trastuzumab, is available for therapeutic use alone or in combination with cytotoxic chemotherapy [82]. Other agents that target HER-2/neu signaling include pertuzumab, ado-trastuzumab emtansine, and the small molecule lapatinib. Pertuzumab is a humanized IgG1 antibody that targets a different epitope on the HER-2/neu receptor than trastuzumab, and this antibody inhibits heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. This drug is used in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer in patients who have not previously received anti-HER chemotherapy for metastatic disease.

Ado-trastuzumab emtansine is an antibody-drug conjugate composed of trastuzumab and the small molecule microtubule inhibitor DM1; it is approved for women with HER2-positive metastatic breast cancer who have received prior therapy with trastuzumab and taxane-based chemotherapy.

Finally, lapatinib is a small molecule inhibitor of the tyrosine kinases associated with EGFR (ErbB1) and HER2 (ErbB2), resulting in inhibition of downstream signaling. This agent is used in combination with the oral fluoropyrimidine capecitabine

for metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy with an anthracycline, a taxane, and trastuzumab.

About 50–60% of patients with metastatic disease respond to initial chemotherapy. A broad range of anti-cancer agents have activity in this disease, including the anthracyclines (doxorubicin, mitoxantrone, and epirubicin) and the taxanes (docetaxel, paclitaxel, and albumin-bound paclitaxel), along with the microtubule inhibitor ixabepilone, navelbine, capecitabine, gemcitabine, cyclophosphamide, methotrexate, and cisplatin. The anthracyclines and the taxanes are two of the most active classes of cytotoxic drugs.

Combination chemotherapy has been found to induce higher and more durable remissions in up to 50–80% of patients, and anthracycline-containing regimens are now considered the standard of care in first-line therapy. With most combination regimens, partial remissions have a median duration of about 10 months and complete remissions have a duration of about 15 months. Unfortunately, only 10–20% of patients achieve complete remissions with any of these regimens, and as noted, complete remissions are usually not long-lasting.

Patients with significant involvement of the lung, liver, or brain and those with rapidly progressive disease rarely benefit from hormonal maneuvers, and initial systemic chemotherapy is indicated in such cases. All breast cancer patients with metastases to the bone should be considered for treatment with a bone-modifying agent (eg, pamidronate, zoledronic acid, or denosumab) because these agents have been shown to decrease the rates of skeletal-related events, such as fractures, spinal cord compression, and pain, and the need for radiation to the bones or surgery [83]. These

agents do not act as anticancer agents and should be coadministered with other therapies targeting the cancer cells specifically.

However, a very low threshold for diagnostic testing exists if any neurologic signs or symptoms occur. Local therapy including surgery, whole-brain radiation, stereotactic radiosurgery or some combination of these approaches are considered as initial therapy. Systemic therapy will continue if the remainder of metastatic sites are stable. If extracranial metastases are progressing, changing the HER2-targeted therapy according to guidelines is appropriate [84].

Radiation Therapy [85]

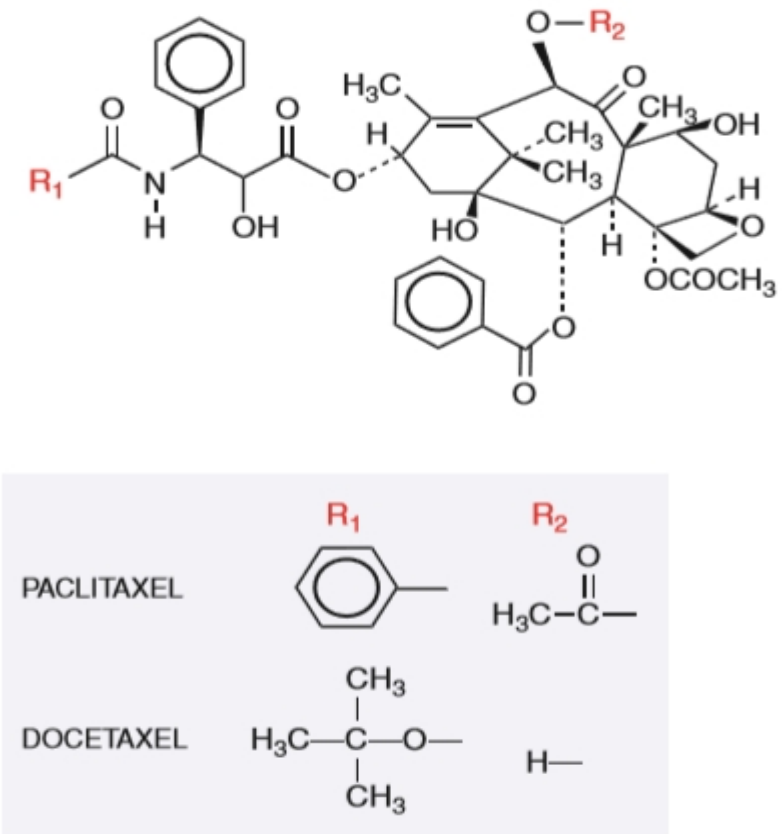
Radiation is an important modality in the treatment of symptomatic metastatic disease. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Radiation therapy provides significant pain relief to about 90% of patients who are treated for painful bone metastases. Radiation is also an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy, as well as eye or orbit lesions and other sites where significant accumulation of tumor cells occurs. Skin and lymph node metastases confined to the chest wall area may also be treated with radiation therapy for palliation (eg, open wounds or painful lesions). Chemotherapy may also be added to radiation for sensitization purposes.

Taxanes [86]

Paclitaxel was first isolated from the bark of the Western yew tree. Paclitaxel and its semisynthetic congeners docetaxel and cabazitaxel, exhibit unique pharmacological properties as inhibitors of mitosis.

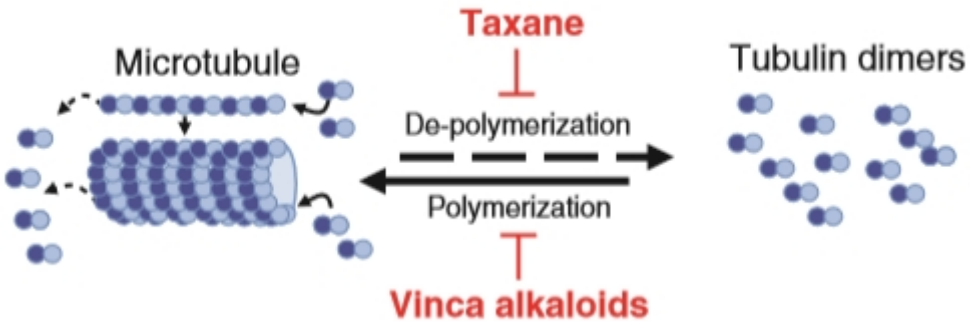
FIGURE.1

CHEMICAL STRUCTURE OF TAXANES



Core structure of taxanes

MECHANISM OF ACTION OF TAXANE



Mechanism of Action

Paclitaxel binds to the β-tubulin subunit on the inner surface of microtubules and antagonizes their disassembly, with the result that bundles of microtubules and aberrant structures derived from microtubules appear in the mitotic phase of the cell cycle ***(figure.2)***. Arrest in mitosis follows. Cell death occurs by apoptosis and depends on both drug concentration and duration of drug exposure.

Drugs that block cell-cycle progression prior to mitosis antagonize the toxic effects of taxanes.

Drug interactions:

The sequence of cisplatin preceding paclitaxel decreases paclitaxel clearance and produces greater toxicity than the opposite schedule.

Paclitaxel decreases doxorubicin clearance and enhances its cardiotoxicity

Docetaxel has no apparent effect on anthracycline pharmacokinetics.

Resistance

Resistance to taxanes can be a result of decreased cellular drug accumulation due to increased expression of membrane-bound efflux proteins, including MRP1 and Pgp. Cabazitaxel is a poor substrate for Pgp and may therefore be useful for treating multidrug-resistant tumors.

Other mechanisms of resistance may include an

- increase in survivin, an antiapoptotic factor
- an increase in α-aurora kinase, which promotes completion of mitosis
- an upregulation of the βIII-isoform of tubulin that lacks taxane-binding capacity
- direct alteration of the drug target by mutation.

Pharmacokinetics

Paclitaxel

- Limited water solubility
- Administered in a vehicle of 50% ethanol and 50% polyethoxylated castor oil.
- Hepatic CYPs (primarily CYP2C8, secondarily CYP3A4) extensively metabolize the drug.
- The primary metabolite is 6-OH paclitaxel, which is inactive
- Multiple additional hydroxylation products are found in plasma
- Less than 10% of a dose is excreted in the urine intact.

- Dose reductions in patients with abnormal hepatic function have been suggested
- About 50%–75% of doses of taxanes should be used in the presence of hepatic metastases larger than 2 cm in size or in patients with abnormal serum bilirubin.
- Drugs that induce CYP2C8 or CYP3A4, such as phenytoin and phenobarbital, or those that inhibit these CYPs, such as antifungal imidazoles, significantly alter drug clearance and toxicity.
- Paclitaxel clearance is nonlinear and decreases with increasing dose or dose rate
- Plasma t1/2 is 10–14 h.
- Critical plasma concentration for myelosuppression depends on the duration of exposure but likely is 50–100 nM.
- Paclitaxel clearance is markedly delayed by cyclosporine A and other drugs that inhibit Pgp.

Nab-paclitaxel

- An albumin-bound nanoparticle solution for infusion (nab-paclitaxel)
- Soluble in aqueous solutions.
- Increased cellular uptake via an albumin-specific mechanism.
- Nab-paclitaxel achieves a higher serum concentration than paclitaxel
- Increased clearance of nab-paclitaxel results in a similar systemic drug exposure.

- Less neurotoxic than paclitaxel
- Approved for metastatic non–small cell lung cancer.
- Should not be given to patients with an absolute neutrophil count below 1500 cells/mm3.

Docetaxel

- More soluble than paclitaxel
- Administered intravenously in an emulsifier (polysorbate 80)
- Absorption: The pharmacokinetic profile is consistent with a three-compartment model. The area under the curve (AUC) was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours.
- Volume of distribution: 113 L
- Protein binding: 97% bound to plasma protein.
- Metabolism: Hepatic. In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme (1 major, 3 minor metabolites).
- Route of elimination: Docetaxel was eliminated in both the urine and feces
- Clearance: 21 L/h/m2
- Elimination t1/2: 12 h.

Therapeutic Uses

The taxanes have become central components of regimens for treating patients with metastatic ovarian, breast, lung, GI, genitourinary, and head and neck cancers.

administered once weekly or once every 3 weeks.

- Cabazitaxel is a poor substrate for Pgp
    - Approved for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

Docetaxel

1. <u>Breast Cancer (BC):</u>

- Single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node positive BC.
- BC locally advanced or metastatic: 60 mg/m2 to 100 mg/m2 single agent.
- BC adjuvant: 75 mg/m2 administered 1 hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 every 3 weeks for 6 cycles

2. <u>Non-Small Cell Lung Cancer (NSCLC):</u>

- Single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC.
- NSCLC: after platinum therapy failure: 75 mg/m2 single agent.
- NSCLC: chemotherapy-naive: 75 mg/m2 followed by cisplatin 75 mg/m2.

3. <u>Hormone Refractory Prostate Cancer (HRPC):</u>

- With prednisone in androgen independent (hormone refractory) metastatic prostate cancer.
- 75 mg/m2 with 5 mg prednisone twice a day continuously.

4. <u>Gastric Adenocarcinoma (GC):</u>

- With cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction.
- 75 mg/m2 followed by cisplatin 75 mg/m2 (both on day 1 only) followed by fluorouracil 750 mg/m2 per day as a 24-hr intravenous infusion (days 1-5), starting at end of cisplatin infusion.

5. <u>Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):</u>

- With cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.
- 75 mg/m2 followed by cisplatin 75 mg/m2 intravenously (day 1), followed by fluorouracil 750 mg/m2 per day as a 24-hr intravenous infusion (days 1-5), starting at end of cisplatin infusion; for 4 cycles

Adverse Effects

1. ***Myelosuppression***
   - Paclitaxel exerts its primary toxic effects on the bone marrow.
   - Neutropenia occurs 8–11 days after a dose & reverses rapidly by 15–21 days.
   - Used with G-CSF, high doses over 24 h are well tolerated
2. ***Peripheral neuropathy*** becomes dose limiting.
3. ***Myalgia***
4. ***Stocking-glove sensory neuropathy*** - In high-dose schedules, or with prolonged use disabling in patients with underlying diabetic neuropathy or concurrent cisplatin therapy.

5. ***Mucositis***

   In 72- or 96-h infusions and in the weekly schedule.

6. ***Hypersensitivity reactions***

   - Paclitaxel infusions of short duration (1–6 h)
   - Largely averted by pretreatment with dexamethasone, diphenhydramine, and histamine H2 receptor antagonists.
   - Premedication is not necessary with 96-h infusions.

7. ***Asymptomatic bradycardia***

8. ***Silent ventricular tachycardia***

   - Occasional episodes
   - Resolve spontaneously during 3- or 24-h infusions.

Nab-paclitaxel

- Increased rates of peripheral neuropathy compared to the original cremophor-delivered paclitaxel
- Rarely causes hypersensitivity reactions.

Docetaxel

- Greater degrees of neutropenia than paclitaxel
- Less peripheral neuropathy and asthenia
- Less frequent hypersensitivity
- Fluid retention - progressive problem with multiple cycles of docetaxel therapy, leading to peripheral edema, pleural and peritoneal fluid, and

pulmonary edema in extreme cases. Oral dexamethasone, begun 1 day prior to drug infusion and continuing for 3 days, greatly ameliorates fluid retention.

- Progressive interstitial pneumonitis – in rare cases
- respiratory failure if the drug is not discontinued.

HER2/Neu Inhibitors [87]

Human epidermal growth factor receptor 2 (also named Neu or ErbB2) is a member of the HER family, which includes also EGFR (HER1), HER3, and HER4.

The fixed conformation of the extracellular domain of HER2 resembles the ligand-activated state of the other HER family members and explains its unique function as a coreceptor that does not require ligand activation. In addition, due to this conformation, the overexpression of wild-type HER2 is sufficient to activate the intracellular tyrosine kinase and oncogenic signaling even in the absence of activating mutations, coreceptors, or ligands.

Overexpression of HER2 is found in 20% to 30% of human breast cancers due to gene amplification on chromosome 17 and results in more aggressive tumors, lower response rates to hormonal therapies, and higher risk of disease recurrence after treatment.

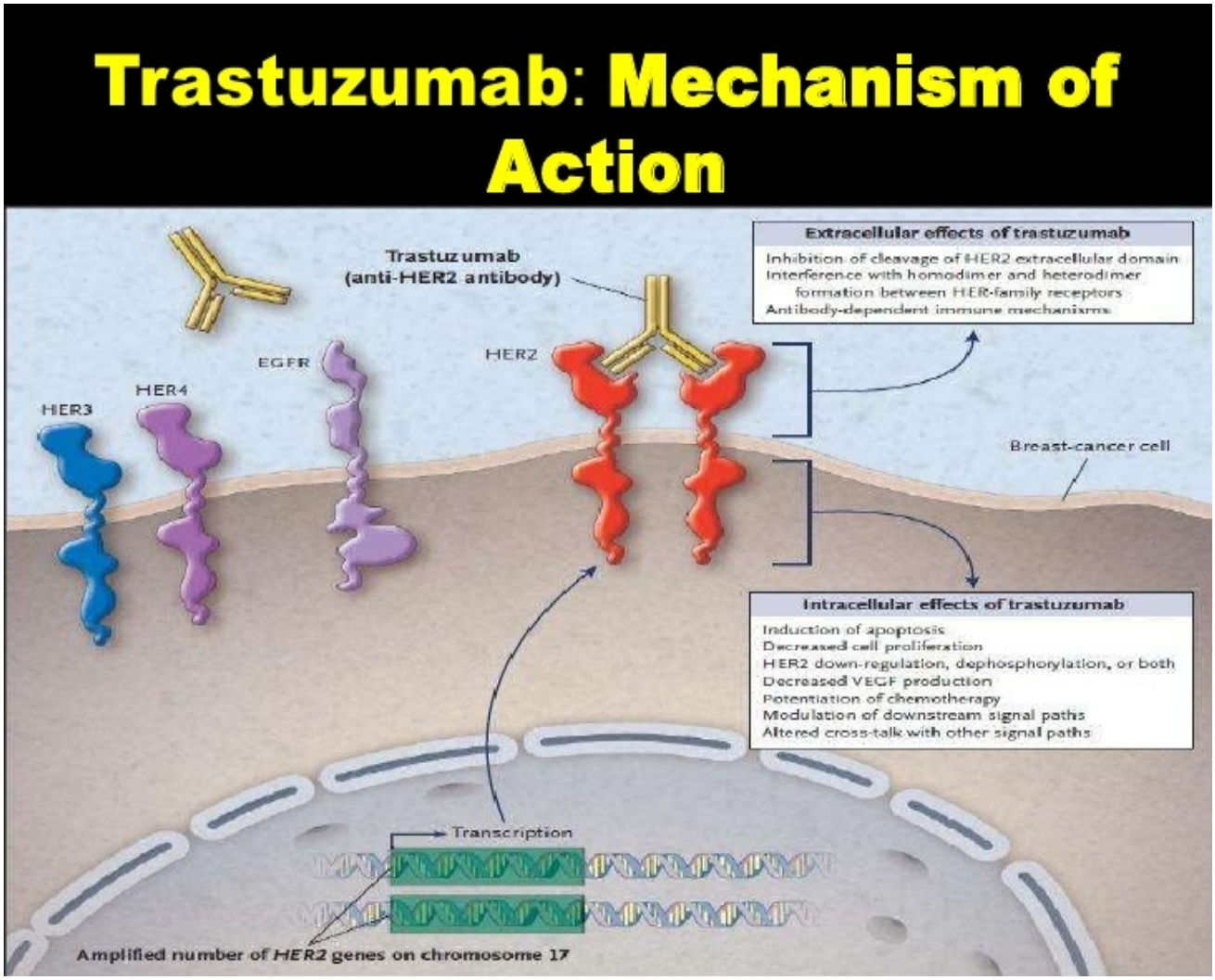
Trastuzumab

FIGURE.3

PROTEIN STRUCTURE OF TRASTUZUMAB

Protein chemical formula: $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$

FIGURE.4



Trastuzumab

Mechanism of Action* (*figure.4)

Trastuzumab is a humanized IgG1 monoclonal antibody that binds to the extracellular domain IV of HER2, inhibiting hetero- and homodimerization and signal transduction.

In addition, binding of trastuzumab to HER2 overexpressing cells can induce antibody-dependent, immune cell–mediated cytotoxicity.

HER2 protein overexpression or gene amplification are predictive of response to HER2-targeted therapies (Wolff et al., 2013).

Pharmacokinetics

- Dose-dependent pharmacokinetics
- Absorption: Peak and trough plasma concentrations at steady state (between weeks 16 and 32) approximately 123 and 79 mcg/mL, respectively.
- Volume of distribution: 44 mL/kg
- Metabolism: Most likely removed by opsonization via the reticuloendothelial system.
- Mean t1/2: 5.8 days on a weekly maintenance dose with alternative dosing every 3 weeks.
- Clearance: Elimination may involve clearance of IgG through the reticuloendothelial system.

Therapeutic Uses

Trastuzumab is approved for HER2-overexpressing breast and gastric cancer.

It is used in combination with cytotoxic chemotherapeutics such as taxanes as initial treatment or as a single agent following relapse of disease after cytotoxic chemotherapy.

1. **Adjuvant Treatment of HER2-Overexpressing Breast Cancer**

Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, (or)

Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30−90 minutes IV infusion every three weeks for 52 weeks.

2. **Metastatic HER2-Overexpressing Breast Cancer**

Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

3. **Metastatic HER2-overexpressing Gastric Cancer**

Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

Adverse Effects and Precautions

Acute adverse effects

- After infusion of trastuzumab are typical for monoclonal antibodies
- Include fever, chills, nausea, dyspnea, and rashes.

Most serious toxicity of trastuzumab is heart failure.

- Cardiotoxicity is caused by interruption of HER2/4 heterodimer signaling in cardiomyocytes, signaling that is essential for the maintenance of contractile function. The cardiotoxic potential was predicted from gene inactivation studies (“knockouts”) in mice, which showed that mice lacking HER2, HER4, or HER ligands developed dilated cardiomyopathy and heart failure.
- Baseline electrocardiogram and cardiac ejection fraction measurement should be obtained before initiating treatment with trastuzumab to rule out underlying heart disease.

- Clinical monitoring for symptoms of congestive heart failure as well as periodic determination of LVEF during and after the course of therapy is recommended.
- When trastuzumab is used as a single agent, fewer than 5% of patients will experience a decrease in LVEF, and about 1% will have clinical signs of congestive failure. However, left ventricular dysfunction occurs in up to 20% of patients who receive a combination of doxorubicin and trastuzumab, reflecting the added cardiotoxicity of doxorubicin.
- In contrast, the risk of cardiac toxicity is greatly reduced with the recommended combination of trastuzumab with taxanes.

RELATED STUDIES

STUDIES ON DOCETXEL IN METASTATIC BREAST CANCER PATIENTS

1. In a phase II trial conducted by Loeffler et al, docetaxel 40 mg/m² was administered once a week for 6 weeks, followed by a 2-week rest. An overall response rate of 47% was reported in 41 metastatic breast cancer patients who had been previously exposed to chemotherapy, including prior paclitaxel. In this study, no cases of grade 2 or greater neutropenia were seen with doses of less than 43 mg/m² per week and grade 2 or higher thrombocytopenia was not observed. In addition to causing minimal hematologic toxicity, the data showed that weekly docetaxel was likely to be associated with a very low incidence of other acute toxicities.

2. In a phase II study by Burstein et al, showed a response rate of 41% in a population of 29 metastatic breast cancer patients treated with weekly docetaxel, 40 mg/m² IV administered over 1 hour. Treatment was administered weekly for 6 weeks, followed by a 2-week rest. Haematological toxicity in this study was minimal. Grade 3 neutropenia occurred in 14% of patients, and grade 4 neutropenia in none. There were no cases of grade 3 or 4 anaemia or thrombocytopenia of any grade. The incidence of non-haematologic toxicity was low, in particular the rate of grade 3/4 neurologic toxicity was very low, with 3% of patients experiencing neuropathy. Fatigue and asthenia occur with prolonged therapy as may fluid retention although at a higher cumulative dose than is seen with every-3-week schedules. A newly reported toxicity of frequent tearing and visual problems, which is generally mild and manageable, may also occur after substantial total exposure to weekly docetaxel, but was not reported at the grade 3/4 level in this trial.
3. Study of weekly docetaxel for the treatment of first- and second-line metastatic breast cancer patients conducted by Stemmler et al in Germany. In the first cycle, patients receive 35 mg/m² per week for 6 consecutive weeks and 2 weeks of rest, followed by treatment for 3 consecutive weeks and 2 weeks of rest. Preliminary results in 33 evaluable patients demonstrate an overall response rate of 36%, with stable disease in an additional 40%. Toxicity data for 40 patients included grade 3 neutropenia (3%), fluid retention (5%), nail toxicity (5%), and lacrimation (5%).

STUDIES ON DOCETAXEL PLUS TRASTUZUMAB IN METASTATIC BREAST CANCER PATIENTS

1. In a study conducted at The University of Texas M.D. Anderson Cancer Center, patients received docetaxel at 35 mg/m² and trastuzumab weekly for 3 weeks, followed by 1 week with no treatment. This study showed a response rate of 63%.
2. Nicholson et al investigated docetaxel at 35 mg/m² given once a week for 6 weeks, followed by 2 weeks of rest. Trastuzumab is given weekly without interruption. The reported response rate to date is 63%.
3. In a study conducted by P.K Jhulka et al, Sixteen women with metastatic breast cancer were treated with trastuzumab (2 mg/kg every week) and docetaxel (100 mg/m2) as first-line therapy. A total of 89 cycles of docetaxel chemotherapy was given (median five cycles per patient). Median number of cycles of trastuzumab was 44 with a range of 20–71. Of the 16 patients, seven (44%) had complete response (CR), whereas five patients (31%) had partial response (PR). The overall response rate (CR+PR) was 75%. Two patients died of progressive disease, and the other two died at home, for which the cause of death could not be known. No anaphylaxis, cardio-toxicity or febrile neutropenia was observed in any patient. Overall, the toxicity was within tolerable limits.

AIM OF THE STUDY

To determine the efficacy and safety of trastuzumab with doxetaxel compared to docetaxel monotherapy in HER2 positive metastatic breast cancer.

METHODOLOGY

STUDY TYPE:

Interventional clinical study.

STUDY DESIGN:

Open labelled, randomized, prospective study.

STUDY PERIOD:

March 2017 - August 2018.

STUDY DURATION:

18 months.

STUDY CENTRE:

Female Medical Oncology ward, Department of Medical Oncology, Tirunelveli Medical College and Hospital, Tirunelveli.

STUDY SAMPLE:

Total of 40 subjects (20 subjects in Trastuzumab & Docetaxel group and 20 subjects in Docetaxel group).

INCLUSION CRITERIA:

1. Female aged 30 to 60 years.
2. Patients with histologically confirmed uni-dimensionally measurable metastatic breast cancer.

3. Patients with Her-2 over-expression as described by Immunohistochemistry (IHC) score of 3＋or 2+ with fluorescence in situ hybridisation (FISH) positive.
4. Stage IV breast cancer
5. Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

EXCLUSION CRITERIA:

1. Patients newly diagnosed with metastatic breast cancer with HER2 -ve status.
2. Patients with white blood cells ≤4,000 cells/mm^3, hemoglobin ≤9.0 g/Dl and platelet count ≤1,00,000cells/mm^3.
3. Patients with aspartate aminotransferase and alanine aminotransferase more than 100 IU/L; and serum creatinine more than or equal to 1.5 times the upper normal limit.
4. Patients with congestive heart failure (CHF).
5. Patients with left ventricular ejection fraction of <45%.
6. Patients with history of myocardial infarction within 6 months before randomization.
7. Patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.
8. Patients with history of prior mediastinal irradiation (except internal mammary-node irradiation for the present breast cancer).
9. Patients with history of hypersensitivity to the Trastuzumab or to drugs with similar chemical structures, or to any of the excipients, or to murine proteins.

10. Patient with history of bleeding disorder, infection and abnormal pulmonary function
11. Patients with any concurrent disease or condition that, in the opinion of the investigator, would make the patient unsuitable for participation in the study.
12. Pregnant women

ETHICAL CONSIDERATION:

- Approval from the Institutional Ethics Committee was obtained.
- Written informed consent in local vernacular language was obtained from every patient before enrolment.

SCREENING AND RECURITMENT:

Patients who fulfilled the eligibility were enrolled after screening with basic investigations like complete blood count, liver function test, renal function test, ECG and ECHO.

Demographic data and history were recorded. Clinical assessment was done for every patient. Kuppuswamy's Socio-economic status scale was used to measure the socio economic status. The baseline characteristics like HER-2 receptor status, prior therapies, metastatic sites before trastuzumab initiation were recorded.

The study participants were allocated either to group 1 or group 2 with the help of computer generated random table.

PROCEDURE:

After randomization, the subjects received the drugs as follows:

Group 1 (n=20)	Group 2 (n=20)
<u>Allocated to intervention:</u> Docetaxel + Trastuzumab <u>Chemotherapy:</u> Docetaxel dose 75mg/m^2 Body surface area I.V infusion once every 21 days for 6 cycles. <u>Trastuzumab:</u> Loading dose- 8mg/kg I.V infusion, followed by maintenance dose- 6mg/kg I.V infusion once every 21 days for 6 cycles.	<u>Allocated to intervention:</u> Docetaxel <u>Chemotherapy:</u> Docetaxel dose 75mg/m^2 Body surface area I.V infusion once every 21 days for 6 cycles.

EFFICACY PARAMETERS

PRIMARY ENDPOINT-

1. Objective response of Cycle 1 and Cycle 6

SECONDARY ENDPOINTS-

1. Subjective response of Cycle 1 and Cycle 6

2. One-year survival

3. One-year progression free survival (PFS)

4. Tolerability and safety profile of the drugs

The following responses were assessed.

1. Objective response:

Objective response rate is defined as the proportion of patients who have a partial or complete response to the therapy. It was evaluated by doing Clinical examination and imaging techniques

- Imaging: X-Ray Chest, USG abdomen
- The Objective tumor response rate was graded from 1 to 4 using the Response Evaluation Criteria in Solid Tumors criteria (RECIST).
- **RECIST (Response Evaluation Criteria in Solid Tumours)**

  1. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

  2. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions from baseline.

3. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

2. Subjective response:

- Subjective evaluation was based on personal interview with patients about the symptoms. The subjective response was graded from 1 to 4 as follows:
    1. Symptom free
    2. Improved
    3. No change
    4. Worse

Patients were asked for the occurrence of any adverse event during or in between the cycles. Laboratory investigations like complete blood count, liver function tests, renal function tests were also done to look for any adverse effect. Patients were provided adverse event diary to note the adverse events. Suspected adverse effects were reported in the predesigned WHO-UMC reporting form to the AMC of Tirunelveli Medical College.

Follow up:

Patients were evaluated at the beginning of every cycle to assess the efficacy and safety of previous cycle. The objective and subjective responses of cycle 1 were assessed at the beginning of the second cycle. Similarly, the responses of the sixth cycle were assessed 1 month after the sixth cycle. Patients were assessed at the end of one year for survival and progression free survival. Complete blood count, liver function tests and renal function tests were repeated before every cycle. ECHO was done at baseline, before third cycle and sixth cycle. CT Scan was done at baseline, after sixth cycle and at the end of one year. One-year survival and the number of patients who had one-year progression free survival were assessed.

3. One-year survival

The number of patients who were alive at the end of one year after the initiation of treatment in both the groups were assessed and percentage was calculated.

4. One-year Progression-free survival (PFS)

Number of patients who survived at the end of one year without disease progression was assessed.

WITHDRAWAL CRITERIA

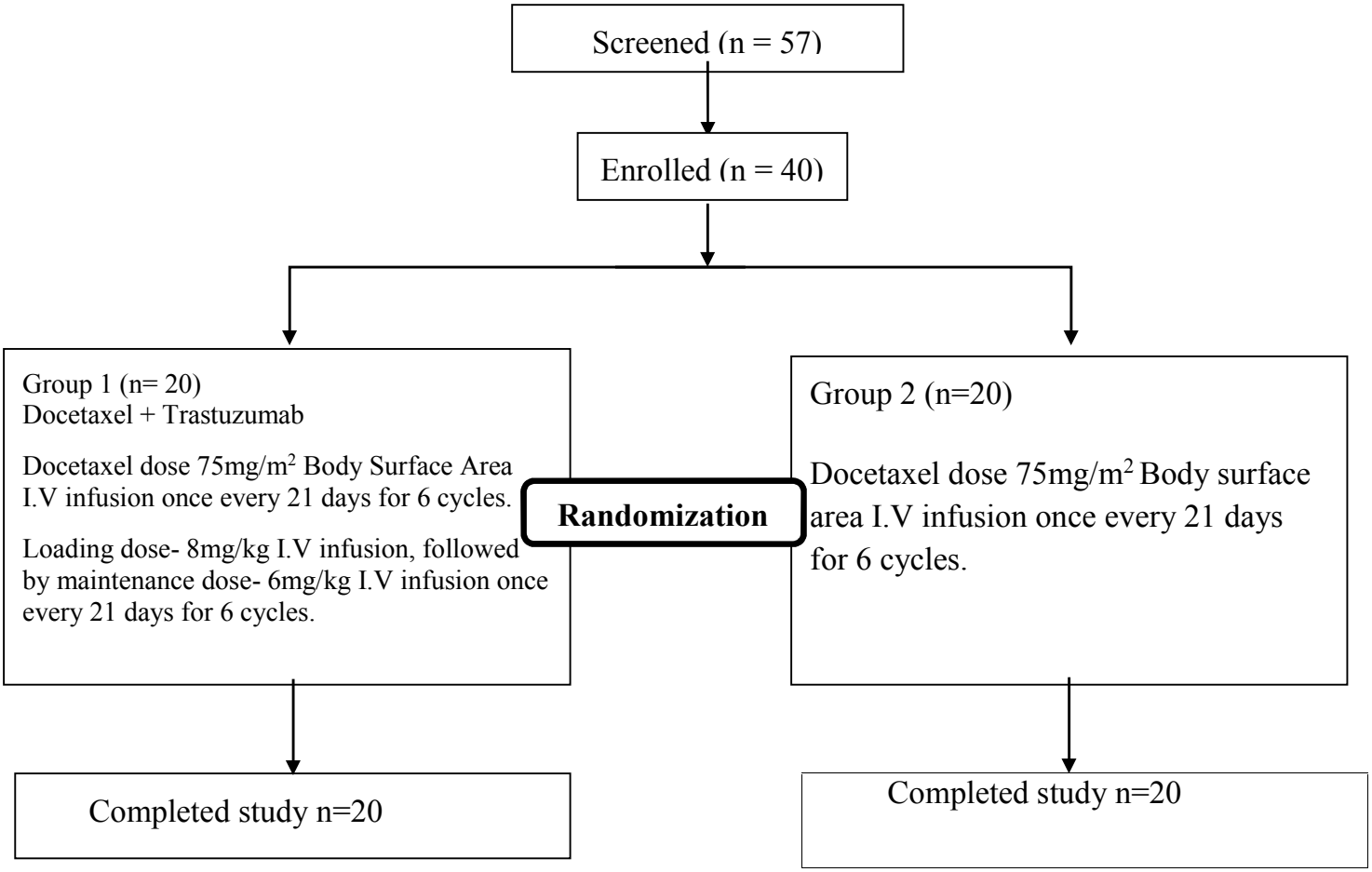
If any of the following adverse effects were observed, Docetaxel was withheld until recovery was confirmed:

- WBC count below 3,000/mm3 & Neutrophil count below 1,500/mm3;
- Neuropathy of grade 2 or more;
- Edema of grade 2 or more; and
- Liver or renal dysfunction of grade 2 or more.

STATISTICAL ANALYSIS:

- Statistical analysis was performed with the help of SPSS (Statistical Package for the Social Sciences) version 20.0
- Mean and Standard deviation were calculated for continuous data while the categorical data were expressed in percentages and in absolute frequencies.
- Baseline demographic characteristics of both the groups were tabulated and matched by Fisher's exact test.
- The efficacy of the individual drugs was analyzed and compared with the help of Mann-Whitney test.
- p value < 0.05 were considered as statistically significant.
- Adverse events were expressed in percentages.

PATIENT DISPOSITION: CONSORT DIAGRAM



RESULTS

Patients admitted in the Female Medical Oncology ward with HER-2 positive Stage IV Metastatic Breast Cancer during the period from March 2017 to May 2018 were screened. Totally 57 subjects were screened out of which, 17 subjects did not meet the eligibility criteria and were excluded. Forty subjects were included in the study and randomly assigned into 2 groups using a computer generated random table. Subjects in Group 1(n=20) received Docetaxel + Trastuzumab and Group 2 (n=20) received Docetaxel monotherapy.

All the randomized subjects completed the study and the results were analyzed.

TABLE- 1

BASELINE PATIENT DEMOGRAPHIC CHARACTERISTICS

Parameters	**Trastuzumab + Docetaxel**	**Docetaxel**	**'p' Value**
Age group (in years)			
<30	0	0	0.645*
31-40	2	3	
41-50	6	9	
51-60	10	7	
>60	2	1	
Locality			
Urban	7	2	0.127*
Rural	13	18	
Socio-economic status			
Upper class	0	0	0.478*
Upper middle class	0	0	
Lower middle class	2	1	
Upper lower class	15	13	
Lower class	3	6	

Fisher's exact test *p value >0.05 - insignificant

Table. 1: shows that there was no significant difference in mean age group, locality and socio-economic status between the study groups.

FIGURE.5

AGE GROUP DISTRIBUTION

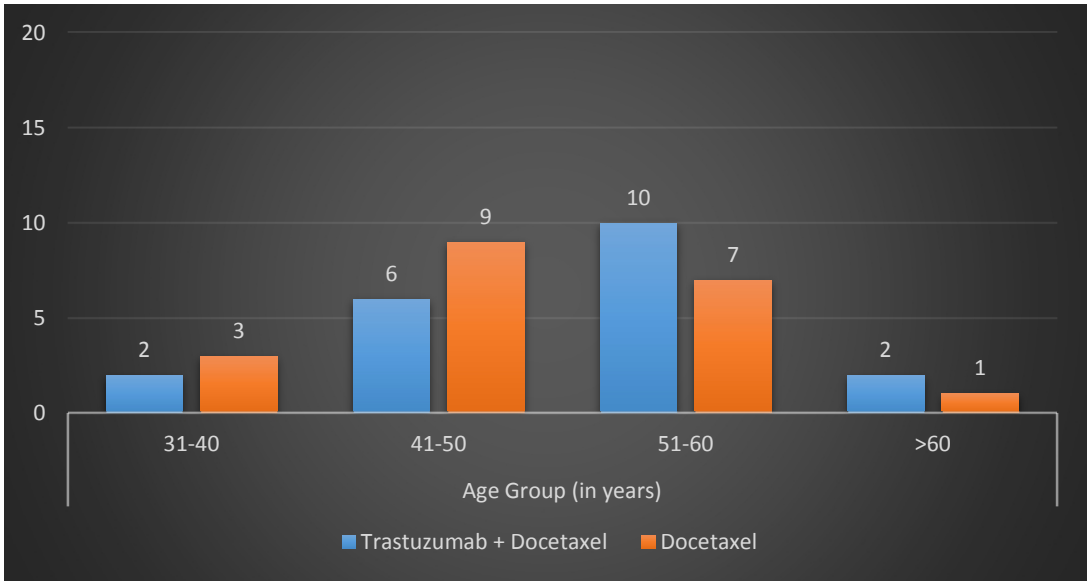


Figure.5: shows the diagrammatic representation of the mean age group of both the study groups.

TABLE- 2

BASELINE PATIENT RISK FACTORS

Parameters	**Trastuzumab + Docetaxel**	**Docetaxel**	**'p' Value**
Obesity			
Yes	3	0	0.231*
No	17	20	
Nulliparity			
Yes	1	0	1.000*
No	19	20	
Family history			
Yes	2	0	0.487*
No	18	20	

Fisher's exact test *p value >0.05 - insignificant

Table. 2: shows that there was no significant difference in risk factors like obesity, nulliparity and family history between both the groups.

TABLE- 3

BASELINE PATIENT CLINICAL CHARACTERISTICS

Parameters	**Trastuzumab + Docetaxel**	**Docetaxel**	**'p' Value**
Number of metastatic sites			
1	14	18	0.248*
2	5	2	
3	1	0	
HER-2 Receptor			
2+	4	2	0.264*
3+	16	18	

Fisher's exact test *p value >0.05 - insignificant

Table. 3: shows that there was no statistical difference between the study groups regarding number of metastatic sites and HER-2 receptor status.

FIGURE.6

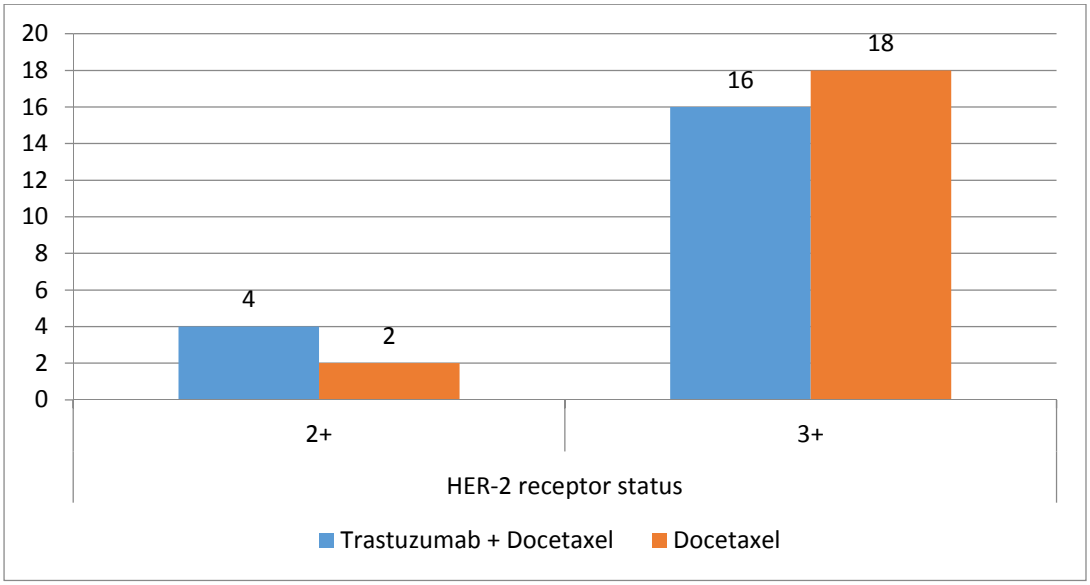


Figure.6: showing the pictorial representation of HER-2 receptor status of both the study groups.

TABLE- 4

BASELINE PRIOR THERAPY

Parameters	**Trastuzumab + Docetaxel**	**Docetaxel**	**'p' Value**
Prior Radiotherapy			
Yes	11	10	0.752*
No	9	10	
Prior Hormonal therapy			
Yes	6	10	0.197*
No	14	10	
Prior Chemotherapy			
Yes	17	13	0.144*
No	3	7	

Fisher's exact test *p value >0.05 - insignificant

Table. 4: shows that the baseline prior therapies like radiotherapy, hormonal therapy and chemotherapy were statistically similar in both the study groups.

TABLE- 5

EFFICACY OF TRASTUZUMAB WITH DOCETAXEL

Parameters	**Duration**	**Mean**	**Standard deviation**	**'p' value**
Objective response	Cycle 1	2.9500	0.22361	0.0001*
	Cycle 6	2.0000	0.00000	
Subjective response	Cycle 1	1.6500	0.87509	0.373
	Cycle 6	1.4500	0.51042	

Mann-Whitney test *p value <0.05 – significant

Table.5: shows the efficacy of Trastuzumab with docetaxel based on objective and subjective responses.

FIGURE.7

EFFICACY OF TRASTUZUMAB WITH DOCETAXEL

Objective response

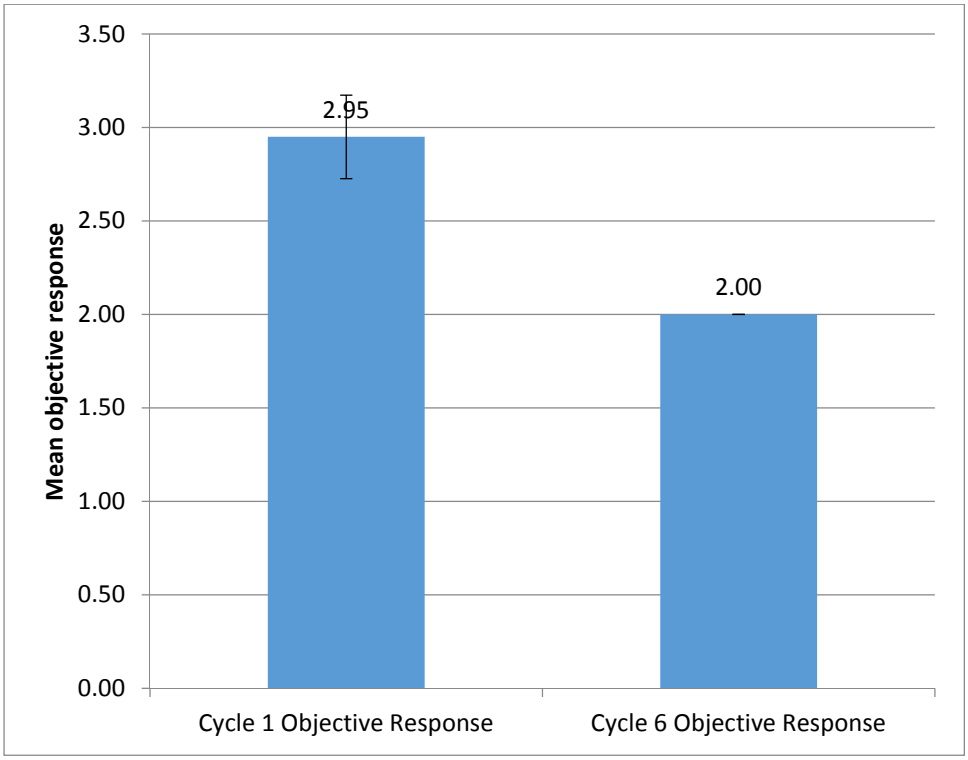


Figure.7: showing the pictorial representation of efficacy of Trastuzumab with docetaxel based on mean objective response.

p value – 0.0001, statistically significant.

Improvement in response from stable disease to partial response was noted.

FIGURE.8

EFFICACY OF TRASTUZUMAB WITH DOCETAXEL

Subjective response

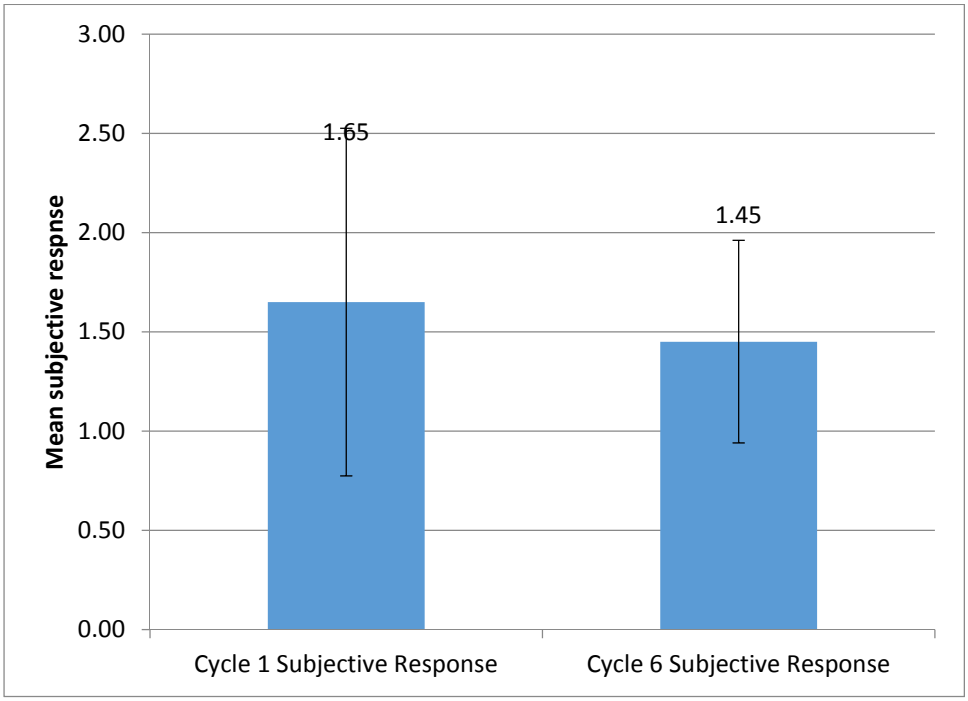


Figure.8: showing the pictorial representation of efficacy of Trastuzumab with docetaxel based on mean subjective response.

p value – 0.373, statistically insignificant

TABLE- 6

EFFICACY OF DOCETAXEL

Parameters	**Duration**	**Mean**	**Standard deviation**	**'p' value**
Objective response	Cycle 1	3.00	0.00	0.0001*
	Cycle 6	2.00	0.00	
Subjective response	Cycle 1	2.80	0.62	0.0001*
	Cycle 6	1.30	0.47	

Mann-Whitney test *p value <0.05 – significant

Table.6: shows that both objective and subjective responses were statistically significant.

FIGURE.9

EFFICACY OF DOCETAXEL

Objective response

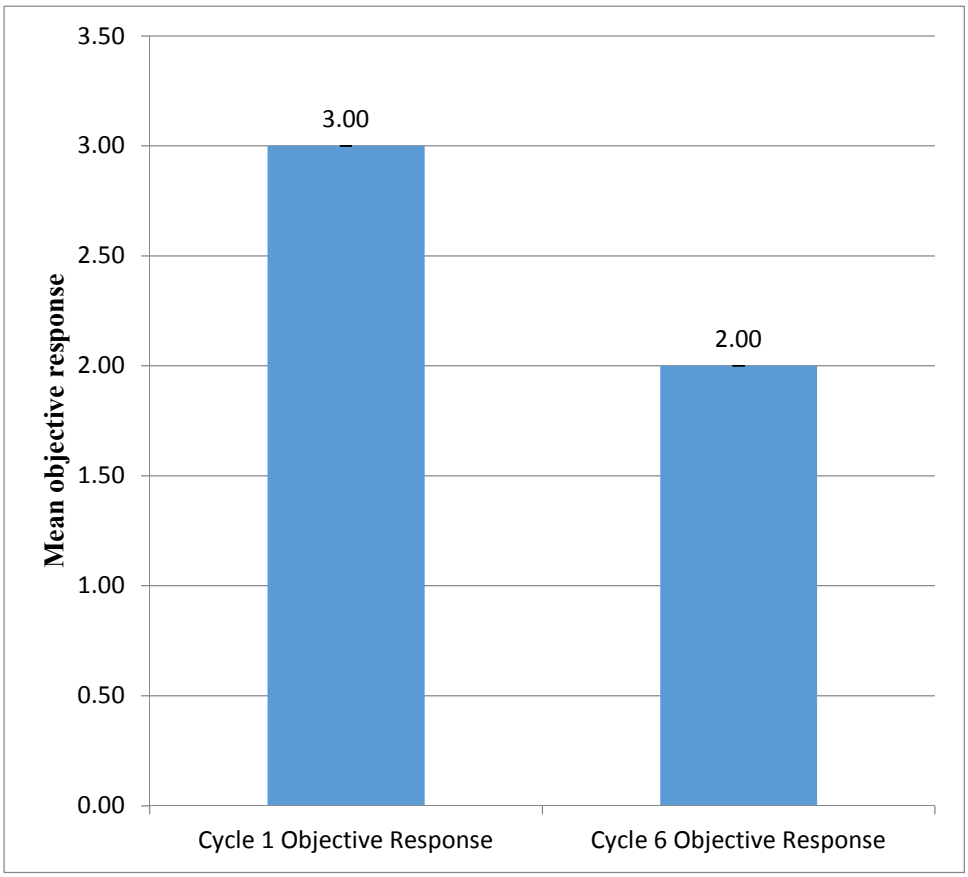


Figure.9: showing the pictorial representation of docetaxel based on mean objective response.

P value – 0.0001, statistically significant.

Improvement in response from stable disease to partial response was noted.

FIGURE.10

EFFICACY OF DOCETAXEL

Subjective response

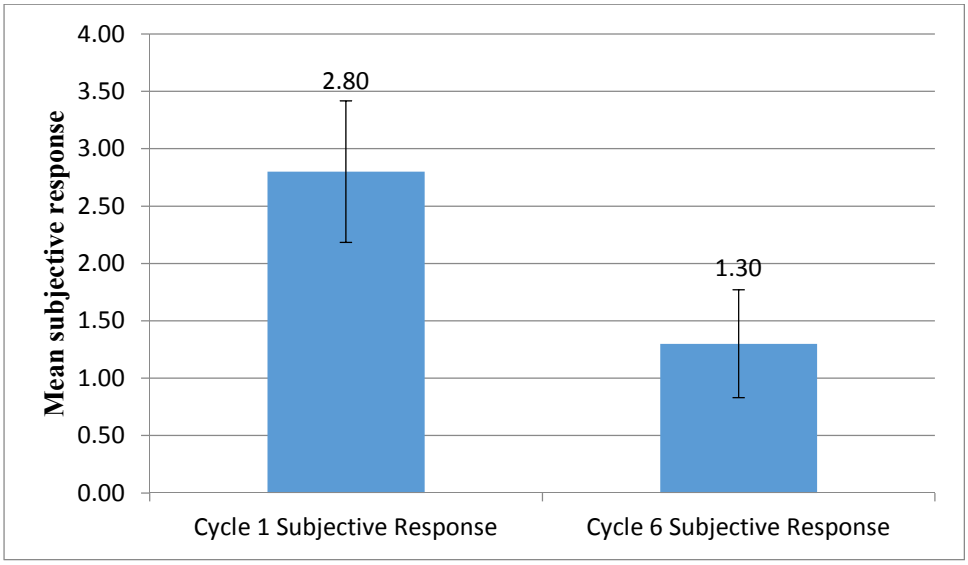


Figure.10: showing the pictorial representation of docetaxel based on mean subjective response.

P value – 0.0001, statistically significant.

Improvement in subjective response was noted.

TABLE- 7

COMPARISON BETWEEN THE EFFICACY OF TRASTUZUMAB WITH DOCETAXEL AND DOCETAXEL

Parameters	**Group**	**Duration**	**Mean**	**Standard deviation**	**'p' value**
Objective response	TRASTUZUMAB + DOCETAXEL	Cycle 1	2.9500	0.22361	0.324
	DOCETAXEL	Cycle 1	3.0000	0.00000	
	TRASTUZUMAB + DOCETAXEL	Cycle 6	2.0000	0.00000	Values are equal
	DOCETAXEL	Cycle 6	2.0000	0.00000	
Subjective response	TRASTUZUMAB + DOCETAXEL	Cycle 1	1.6500	0.87509	0.00001*
	DOCETAXEL	Cycle 1	2.8000	0.61559	
	TRASTUZUMAB + DOCETAXEL	Cycle 6	1.4500	0.51042	0.340
	DOCETAXEL	Cycle 6	1.3000	0.47016	

Mann-Whitney test *p value >0.05 – significant

Table.7: shows the comparison between the efficacy of trastuzumab with docetaxel and docetaxel of cycle 1 and cycle 6

Objective response:

Objective response of first cycle and sixth cycle were similar in both the groups.

Subjective response:

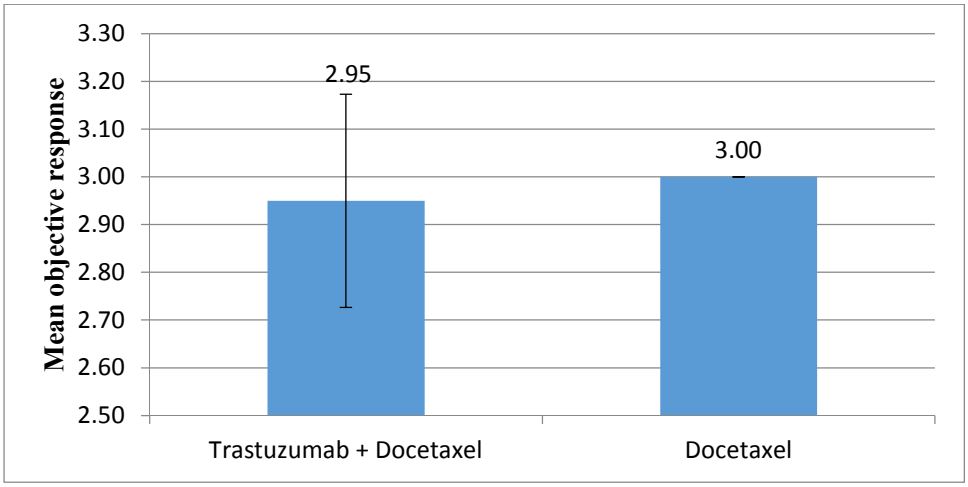
Subjective response of first cycle was statistically significant in the Trastuzumab with docetaxel group when compared to the docetaxel monotherapy group.

There was no significant difference in subjective response after sixth cycle between both the study groups.

FIGURE.11

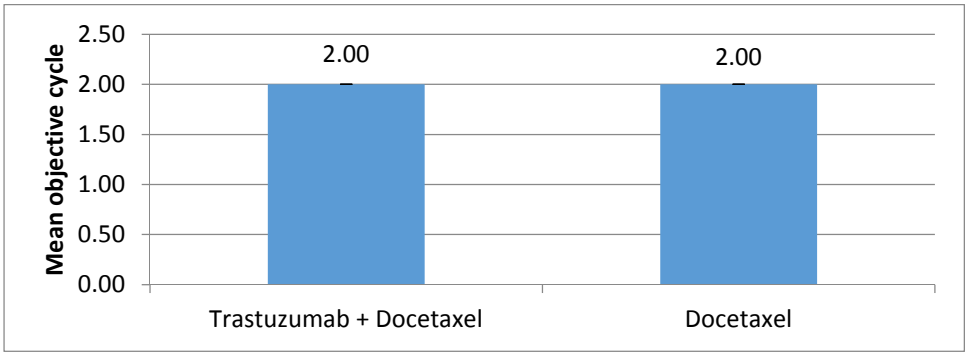
COMPARISON BETWEEN THE EFFICACY OF TRASTUZUMAB WITH DOCETAXEL AND DOCETAXEL

Objective response of Cycle 1:



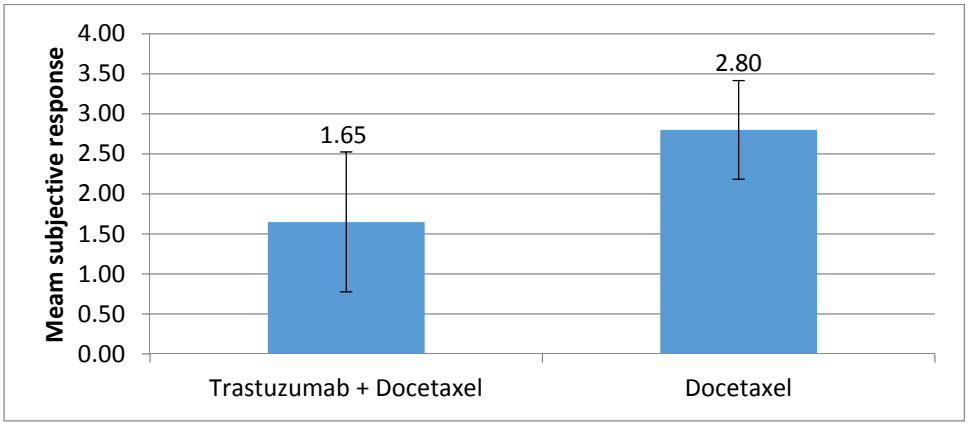
p value – 0.324, statistically insignificant.

Objective response of Cycle 6:



Comparison of mean objective response between the efficacy of Trastuzumab with docetaxel and docetaxel of cycle 6. No significant difference noted.

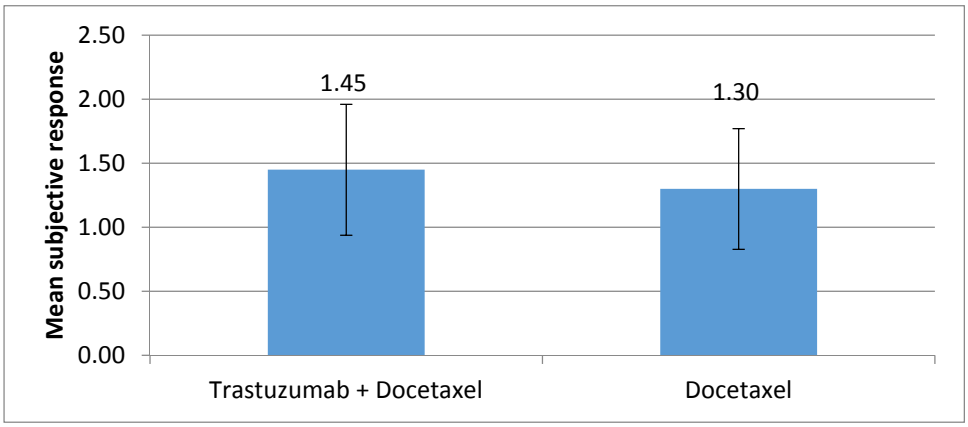
Subjective response of cycle 1:



p value – 0.00001, statistically significant.

Improvement in subjective response was significant in Trastuzumab with docetaxel than docetaxel.

Subjective response of cycle 6:



p value – 0.340, statistically insignificant

TABLE-8

ONE-YEAR SURVIVAL AND ONE-YEAR PROGRESSION FREE SURVIVAL

GROUP	**ONE-YEAR SURVIVAL**	**DEATH**	**ONE-YEAR PROGRESSION FREE SURVIVAL**
TRASTUZUMAB + DOCETAXEL n=20 (%)	16 (80%)	4 (20%)	12 (60%)
DOCETAXEL n=20 (%)	12 (60%)	8 (40%)	7 (35%)

Table-8: shows the comparison between the one-year survival, death and one-year progression free survival in both the Trastuzumab with docetaxel and the docetaxel group.

Results showed that more number of patients in the Trastuzumab with docetaxel group survived one year and also had progression free survival at the end of one year when compared to Docetaxel monotherapy.

TABLE-9

ADVERSE DRUG REACTION COMPARISON

ADVERSE EVENT	**TRASTUZUMAB + DOCETAXEL (N=20) (%)**	**DOCETAXEL (N=20) (%)**
Haematological	**65%**	**55%**
Leukopenia	8 (40%)	7 (35%)
Anaemia	5 (25%)	4 (20%)
Non-haematological	**35%**	**45%**
Alopecia	3 (15%)	3 (15%)
Peripheral neuropathy	2 (10%)	3 (15%)
Myalgia/arthralgia	1 (5%)	2 (10%)
Nail discolouration	1 (5%)	1 (5%)

Table – 9: shows the adverse drug reactions that occurred during the study period.

FIGURE.12

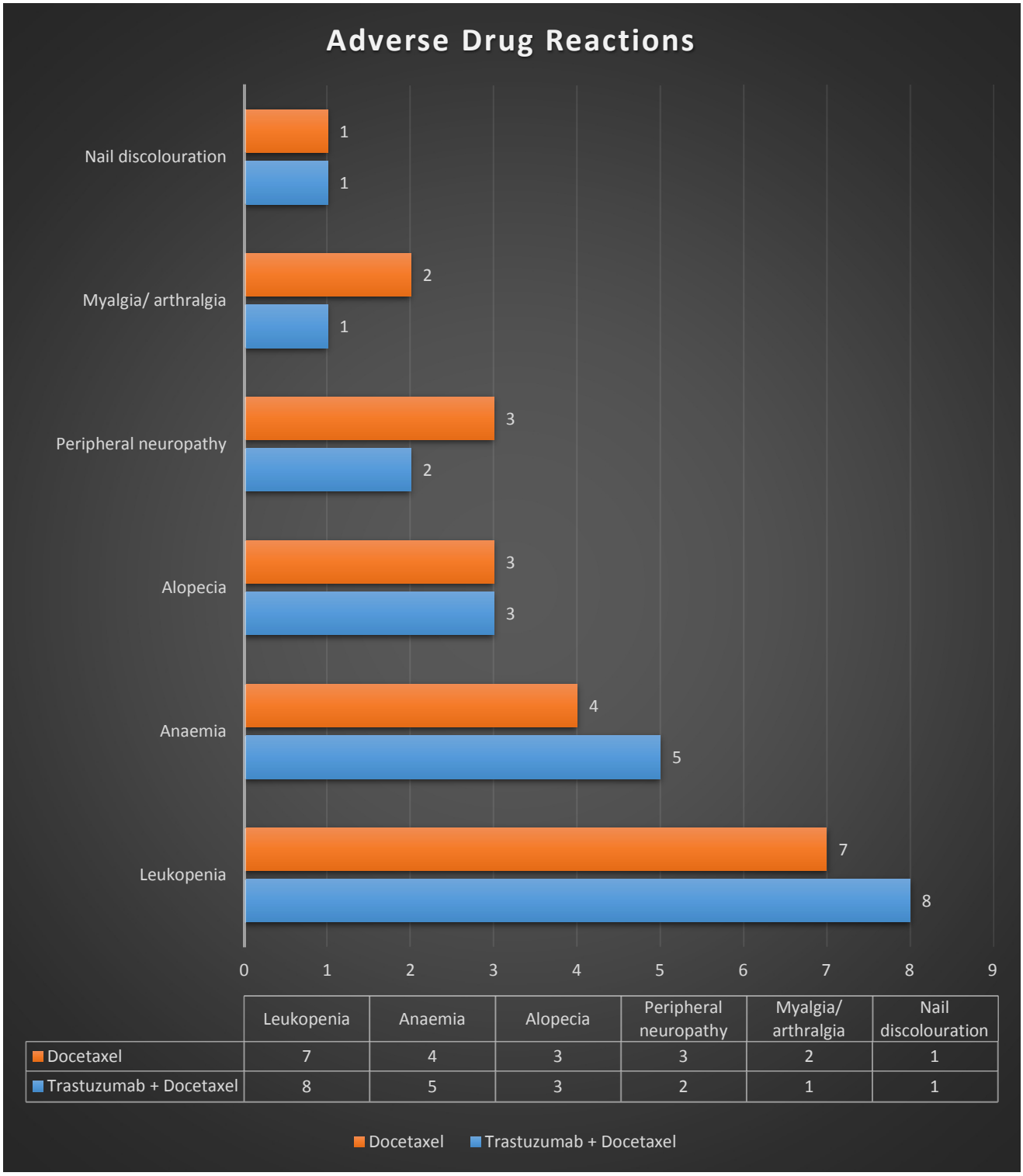


Figure.12: Pictorial representation of the adverse drug reactions that occurred during the study period.

DISCUSSION

Results in the treatment of metastatic breast cancer continue to be poor, despite developments in chemotherapeutic treatment. In developing countries like India, a significant number of patients with breast cancer present with metastatic disease. In the past two decades, drugs like paclitaxel, docetaxel, vinorelbine and capecitabine are increasingly being employed for the locally advanced and metastatic breast cancer. Laboratory studies have shown that HER-2 gene amplification is a poor prognostic factor. The HER-2 receptor serves as a target for the therapeutic manipulations with Monoclonal Antibodies.

Trastuzumab is one of the first targeted biologics for the treatment of solid tumours. Owing to its unique mechanism of action and minimal toxicity associated with it, trastuzumab is the ideal partner for chemotherapy and there is much interest in combining it with various chemotherapeutic agents. Slamon et al. [88] carried out a multivariate analysis of earlier studies and observed that HER-2 overexpression was associated with increased responsiveness to paclitaxel or docetaxel. This makes the trastuzumab and taxanes an attractive combination for the treatment of breast cancer. Surprisingly, docetaxel has shown better effect compared with paclitaxel [89].

The present study evaluated the efficacy and safety of trastuzumab and docetaxel combination versus docetaxel monotherapy in the management of HER-2 positive metastatic breast cancer. The mean age of the subjects in both groups fall under the age group of 41-60 years which is similar to studies conducted by P.K. Julka et al [90].

In this study, majority of the subjects in both groups belonged to rural population (Trastuzumab with Docetaxel- 65% and Docetaxel 90%). About 75% of the subjects in

the Trastuzumab with Docetaxel group and 65% in the Docetaxel group belonged to upper lower class socioeconomic status**.** HER-2 receptor overexpression (IHC score 3+) was seen in 80% of the subjects in Trastuzumab with Docetaxel group and 90% of the subjects in Docetaxel group.

Most patients in both the groups had undergone prior chemotherapy which is similar to the studies similar to Nobuaki Sato et al [(91)]. About half of the patients received prior radiotherapy in both groups. As far as prior hormonal therapy is concerned 30% had received in Trastuzumab with Docetaxel group and 50% in Docetaxel group.

Objective response

Objective tumor response rate was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST).

All patients in Trastuzumab with docetaxel group had stable disease at the beginning of second cycle which showed their good response to the first cycle. One month after sixth cycle most of the patients improved one grade ahead (from stable disease to partial response) in this group.

All patients in docetaxel group had stable disease at the beginning of second cycle showing that the first cycle of chemotherapy was effective. At one month after sixth cycle the improvement was one grade ahead as seen in the other group (i.e., from stable disease to partial response).

When Objective responses of Trastuzumab with Docetaxel combination and Docetaxel monotherapy were compared at the end of first cycle and sixth cycles, they were found to be similar without any significant difference between the study groups.

Both groups had shown partial response (PR) in the objective response at the end of sixth cycle.

Subjective response

At the beginning of second cycle when the patients were asked for the subjective response, 55% of patients had improved from baseline and 45% were symptom free. It showed subjectively also they had a very good response to first cycle of Trastuzumab with docetaxel. But when subjective responses were compared between cycle 1 and 6, there was no much difference.

In patients who were on docetaxel monotherapy, 30% of patients had improved from baseline and 70% were symptom free. Whereas the subjective response after sixth cycle didn't show any statistical difference when compared to that of cycle 1. Hence very good subjective responses to cycle 1 and insignificant difference in subjective responses between cycle 1 and cycle 6 in both the groups, indicate that both the regimens produced earlier subjective responses which were maintained throughout upto cycle 6.

The Subjective responses of cycle one and cycle six between both groups were compared. Trastuzumab with docetaxel showed better subjective response after first cycle. Subjective responses after sixth cycle were found to be similar in both the groups.

The other secondary endpoints were one-year survival, death and one-year progression free survival. More number of patients (80%) in trastuzumab with docetaxel group survived after one year when compared to docetaxel monotherapy (60%). About 60% of patients in Trastuzumab with docetaxel group showed progression free survival

at the end of first year whereas 35% of patients only had progression free survival at the end of first year in docetaxel group.

No subject discontinued the drug due to any adverse event. Side-effects were similar in both the study groups. The most common hematological toxicity was leukopenia. Almost all patients with leukopenia were manageable by reducing the dose of docetaxel or treatment with G-CSF alone. Neither leukopenia nor anaemia led to treatment discontinuation. The toxicity pattern is consistent with the other published studies. Like other studies [92,93,94], haematological toxicity was the commonest toxicity in this study. Non-Haematological toxicities reported were alopecia, peripheral neuropathy, myalgia/arthralgia and nail discolouration and they were almost equal in both the study groups.

Limitations:

This study was conducted with a small sample size and followed upto one year only. Overall survival, overall response rate and time to progression could not be made out in this study due to short term follow-up period.

CONCLUSION

Although the objective responses of cycle 1 & 6 and subjective response of cycle 6 were similar in both the groups, one-year survival and progression free survival were better with the combination of Trastuzumab and docetaxel. Subjective response of first cycle was also better in this group compared to docetaxel monotherapy. Owing to the high cost, many patients in India may not be able to afford Trastuzumab. But it is certainly a promising combination with metastatic breast cancer in patients with HER-2-overexpression. Further long term studies regarding overall survival, overall response rate and time to progression would be needed to confirm the effectiveness of this combination over docetaxel monotherapy in the metastatic setting.

APPENDIX –I

INFORMED CONSENT FORM

Study Title:

TRASTUZUMAB AND DOCETAXEL COMBINATION THERAPY COMPARED TO DOCETAXEL MONOTHERAPY IN HER2-POSITIVE STAGE IV METASTATIC BREAST CANCER – AN OPEN LABELLED RANDOMIZED STUDY

Study Number _____

Subject's Full Name _____

Date of Birth/Age_____

Address _____

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. **OR** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf,the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legal Representative: _____

Signatory's Name _____Date _____

Signature of the Investigator _____ Date _____

Study Investigator's Name _____ Date _____

Signature of the Witness _____Date _____

Name of the Witness

மருத்துவ ஆய்வில் பங்கேற்க நோயாளிகளுக்கான அறிவிப்பு மற்றும் ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு:

வேற்றிடப் பதியம் மார்ப்பகம் புற்றுநோய்க்கு டிராசுடுசுமாபுடன் டோகிடாக்சல் சேர்த்து மற்றும் டோகிடாக்சல் தனி மருந்தாகவும் கொடுப்பதால் ஏற்படும் முன்னேற்றம் மற்றும் பக்கவிளைவுகளைப் பற்றிய ஒப்பீட்டு ஆய்வு.

பங்குபெறுபவரின் பெயர்:
பங்குபெறுபவரின் வயது:

1. நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்துகொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது எனவும் அறிந்துகொண்டேன்.
2. நான் இவ்வாய்வில் தன்னிச்சையாக மட்டுமே பங்கேற்கிறேன். எந்த காரணத்தினாலோ, எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்விலிருந்து விலகிக்கொள்ளலாம் என்றும் அறிந்துகொண்டேன்.
3. இந்த ஆய்வு சம்பந்தமாகவோ, இதைச்சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என்னுடைய அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன். நான் ஆய்விலிருந்து விலகிக்கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.
4. இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்கமாட்டேன்.
5. இந்த ஆய்வில் பங்குகொள்ள முழுமனதோடு ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்துகொள்வதுடன் ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன். என் உடல்நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் /ரேகை.....
இடம்..... தேதி.....
பங்கேற்பவரின் பெயர் மற்றும் விலாசம்.....
.....
ஆய்வாளரின் பெயர், கையொப்பம்.....
சாட்சியின் கையொப்பம் மற்றும் விலாசம் (கல்வியறிவு இல்லாதவர்க்கு)

APPENDIX – II

RECIST (Response Evaluation Criteria in Solid Tumours)

1. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

2. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions from baseline.

3. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

APPENDIX - III

STUDY PROFOMA

Patients characteristics:

Name: _____

Age: _____years

IP.No: _____

Locality: (a)Urban (b)Rural

Address:

_____

_____

Phone number: _____

Education: (a)illiterate (b)Primary (c)High school and higher secondary (d)diploma & degree (d)professional

Occupation: (a)unemployed (b)unskilled (c)semi-skilled (d)skilled (e)professional

Socio-economic status: (a)lower (b)middle (c)upper

Religion: (a)Hindu (b)Christian (c)Muslim

Marital status: (a)single (b)married (c) separated or widowed

Substance abuse in past one year: (a)smoker (b)alcohol (c)tobacco chewing (d)none

Medical co-morbidity: (a)Diabetes (b)Hypertension (c)coronary heart disease (d)others

Reproductive and menstrual history:

Age at menarche: _____years

Total no. of full term pregnancies: (a)0 (b)1 (c)2 (d)≥3

Attained menopause: (a)yes (b)no

If yes, age at menopause: _____years

Family history: (a)yes (b)no

Diagnosis:

_____

Date of diagnosis: _____

Stage at diagnosis:

_____

No of positive lymph nodes at diagnosis: (a)1 (b)2 (c)3 (d)≥4

No of Metastatic sites at enrolment: (a)1 (b)2 (c)3 (d)≥4

Metastatic sites at enrolment: _____

Degree of over-expression of HER-2: (a)2+ (b)3+

Prior treatment

Prior radiotherapy: (a)yes (b)no

If yes, (a)as adjuvant (b)for metastasis (c)for both

Prior hormonal therapy: (a)yes (b)no

If yes, (a)as adjuvant (b)for metastasis (c)for both

Prior Chemotherapy: (a)yes (b)no

If yes, (a)Anthracycline-based_____

(b)Non-anthracycline-based_____

General examination

Weight:

Height:

BMI:

Pulse rate:

Blood pressure:

Investigations

Complete blood count

Total blood count:

Differential count:

Haemoglobin:

Platelet count:

Renal function test

Blood Urea:

Serum Creatinine:

Serum sodium:

Serum potassium:

Blood sugar (F):

Blood sugar (PP):

Fasting Lipid profile

Total cholesterol:

Serum triglyceride:

LDL:

VLDL:

HDL:

Total cholesterol / HDL ratio

TGL / HDL ratio:

Liver function test

Total bilirubin:

Direct bilirubin:

Indirect bilirubin:

SGOT:

SGPT:

Alkaline phosphatise:

Total protein:

ECHO:

Special investigations:

Treatment:

S.No	Name of drug	Dose	No of cycle	Route

Treatment efficacy:

1. Subjective response
   subjective evaluation was based on a personal interview about the symptoms.
   (a)symptom-free (b)improved (c)no change (d)worse
2. Objective response
   (a)complete response (b)partial response (c)stable disease (d)progressive disease
3. One-year survival (OS)
4. One-year Progression-free survival (PFS)

Adverse events:

TYPE OR LOCATION OF ADVERSE EVENT	
Any type	
Abdominal pain	
Asthenia	
Back pain	
Chest pain	
Chills	
Fever	
Headache	
Infection	
Pain	

Cardiovascular system	
Heart failure	
>10% relative reduction in LVEF	
Digestive tract	
Anorexia	
Constipation	
Diarrhea	
Nausea	
Stomatitis	
Vomiting	
Hematologic and lymphatic systems	
Anemia	
Leukopenia	
Neutropenia	
Thrombocytopenia	
Musculoskeletal system	
Arthralgia	
Myalgia	
Hand foot syndrome	
Nervous system	
Paresthesia	
Neuropathy	

Respiratory tract	
Increased coughing	
Dyspnea not related to heart failure	
Pharyngitis	
Skin	
Alopecia	
Rash	
Elevated serum creatinine	
Elevated serum transaminases	
Electrolyte abnormalities	
Menstrual irregularities	
OTHERS	

APPENDIX – 4

MASTER CHART

Trastuzumab with Docetaxel combination

Sl No	GROUP 1-T+D 2-D	AGE GROUP <30-1, 31-40:2, 41-50:3, 51-60:4, >60:5	LOCALITY urban-1, rural-2	Socio Economic status Upper class- 1, UMC-2, LMC-3, ULC-4, Lower class-5	OBESITY yes-1, no-2	NULLIPARITY/ >30years YES-1, NO-2	FAMILY HISTORY YES-1, No-2	METASTATIC SITES 1, 2, 3	HER2 2+: 1, 3+: 2	PRIOR Radio therapy yes- 1, no-2	PRIOR Hormonal Therapy yes-1, no-2	PRIOR Chemo Therapy yes-1, no-2	C1 Objective response complete-1, partial-2, stable-3, progressive-4	C6 Objective response complete-1, partial-2, stable-3, progressive-4	C1 Subjective response symptom free-1, improved-2, no change-3, worse-4	C6 Subjective response symptom free-1, improved-2, no change-3, worse-4
1	1	3	2	4	2	2	2	1	1	1	1	1	3	2	1	2
2	1	4	2	4	1	2	2	1	2	1	2	1	3	2	1	1
3	1	4	1	3	2	2	2	3	2	2	2	1	3	2	1	2
4	1	3	2	5	2	2	2	1	2	1	2	1	3	2	1	2
5	1	4	2	4	2	2	2	1	2	1	2	1	3	2	1	2
6	1	5	1	5	2	2	2	1	2	1	1	1	3	2	1	2
7	1	4	2	4	2	1	2	2	1	1	1	1	3	2	1	2
8	1	3	1	4	2	2	2	2	2	2	2	1	3	2	1	1
9	1	2	2	4	2	2	2	2	2	2	2	1	3	2	3	1
10	1	4	2	4	2	2	1	2	1	1	2	1	3	2	2	1

T- Trastuzumab, D- Docetaxel

Trastuzumab with Docetaxel combination

Sl No	GROUP 1-T+D 2-D	AGE GROUP <30-1, 31-40:2, 41-50:3, 51-60:4, >60:5	LOCALITY urban-1, rural-2	Socio Economic status Upper class- 1, UMC-2, LMC-3, ULC-4, Lower class-5	OBESITY yes-1, no-2	NULLIPARITY/ >30years YES-1, NO-2	FAMILY HISTORY YES-1, No-2	METASTATIC SITES 1, 2, 3	HER2 2+: 1, 3+: 2	PRIOR Radio therapy yes- 1, no-2	PRIOR Hormonal Therapy yes-1, no-2	PRIOR Chemo Therapy yes-1, no-2	C1 Objective response complete-1, partial-2, stable-3, progressive-4	C6 Objective response complete-1, partial-2, stable-3, progressive-4	C1 Subjective response symptom free-1, improved-2, no change-3, worse-4	C6 Subjective response symptom free-1, improved-2, no change-3, worse-4
11	1	5	1	4	2	2	1	1	2	2	1	1	2	2	2	1
12	1	2	1	4	1	2	2	1	2	1	2	1	3	2	2	1
13	1	3	2	3	2	2	2	1	2	2	2	2	3	2	3	1
14	1	4	1	4	2	2	2	1	2	2	2	2	3	2	3	1
15	1	3	1	4	2	2	2	1	2	2	2	2	3	2	3	1
16	1	4	2	4	2	2	2	1	2	1	2	1	3	2	1	2
17	1	4	2	4	1	2	2	1	2	1	1	1	3	2	1	2
18	1	4	2	5	2	2	2	1	1	1	1	1	3	2	1	2
19	1	3	2	4	2	2	2	2	2	2	2	1	3	2	1	1
20	1	4	2	4	2	2	2	1	2	2	2	1	3	2	3	1

T- Trastuzumab, D- Docetaxel

Docetaxel monotherapy

Sl No	GROUP 1-T+D 2-D	AGE GROUP <30-1, 31-40:2, 41-50:3, 51-60:4, >60:5	LOCALITY urban-1, rural-2	Socio Economic status Upper class- 1, UMC-2, LMC-3, ULC-4, Lower class-5	OBESITY yes-1, no-2	NULLIPARITY/ >30years YES-1, NO-2	FAMILY HISTORY YES-1, No-2	METASTATIC SITES 1, 2, 3	HER2 2+: 1, 3+: 2	PRIOR Radio therapy yes- 1, no-2	PRIOR Hormonal Therapy yes-1, no-2	PRIOR Chemo Therapy yes-1, no-2	C1 Objective response complete-1, partial-2, stable-3, progressive-4	C6 Objective response complete-1, partial-2, stable-3, progressive-4	C1 Subjective response symptom free-1, improved-2, no change-3, worse-4	C6 Subjective response symptom free-1, improved-2, no change-3, worse-4
21	2	2	1	4	2	2	2	1	2	2	2	2	3	2	1	1
22	2	4	2	5	2	2	2	1	1	2	2	2	3	2	3	2
23	2	4	2	4	2	2	2	1	1	2	2	1	3	2	3	2
24	2	4	2	4	2	2	2	1	2	2	1	1	3	2	3	1
25	2	3	2	5	2	2	2	1	2	1	1	1	3	2	3	2
26	2	4	2	4	2	2	2	1	2	1	1	1	3	2	3	1
27	2	2	2	4	2	2	2	1	2	2	1	1	3	2	3	2
28	2	3	2	4	2	2	2	1	2	1	1	2	3	2	3	2
29	2	3	2	5	2	2	2	1	2	1	1	1	3	2	3	1
30	2	3	2	4	2	2	2	1	2	2	2	2	3	2	3	1
31	2	4	2	5	2	2	2	2	3	2	2	2	3	2	3	1
32	2	4	2	4	2	2	2	1	2	1	1	1	3	2	3	1
33	2	3	2	4	2	2	2	1	2	2	1	1	3	2	3	1
34	2	5	2	4	2	2	2	1	3	1	2	1	3	2	3	1
35	2	3	2	5	2	2	2	2	2	2	2	2	3	2	3	1
36	2	3	1	4	2	2	2	1	2	1	2	1	3	2	3	1
37	2	4	2	4	2	2	2	1	2	1	2	1	3	2	3	1
38	2	3	2	4	2	2	2	1	2	1	1	1	3	2	3	1
39	2	2	2	5	2	2	2	1	2	1	1	1	3	2	1	2
40	2	3	2	3	2	2	2	1	2	2	2	2	3	2	3	1

T- Trastuzumab, D- Docetaxel

APPENDIX – V

ABBREVIATIONS

ACS - American Cancer Society

AJCC - American Joint Committee for Cancer

ASCO - American Society of Clinical Oncology

BMI - Body mass index

BSE - Breast self-examination

CDK - cyclin-dependent kinases

DCIS - Ductal carcinoma in situ

DFS - Disease-free survival

DVT - Deep-vein thrombosis

ER - Estrogen receptor

ESBC - Early stage breast cancer

ESMO - European Society of Medical Oncology

FDA - Food and Drug Administration

FISH - Fluorescence in situ hybridization

HER2 - Human epidermal growth factor receptor-2

HRT - Hormone replacement therapy

IBC - Inflammatory breast cancer

IHC - Immunohistochemistry

LCIS - Lobular carcinoma in situ

MBC - Metastatic breast cancer

MoAB - Monoclonal antibody

mTOR - Mammalian target of rapamycin

NCCN - National Comprehensive Cancer Network

NCI - National Cancer Institute

OS - Overall survival

pCR - pathologic Complete Response

PFS - Progression-free survival

PI3K - Phosphatidylinositol 3-kinase

PR - Progesterone receptor

SERM - Selective estrogen receptor modulators

SLNB - Sentinel lymph node biopsy

TKI - Tyrosine kinase inhibitor

TNBC - Triple negative breast cancer

VEGF - Vascular endothelial growth factor

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